RING-OPENING METATHESIS/CROSS METATHESIS AND DOMINO METATHESES OF 8-OXABICYCLO[3.2.1]OCTENE DERIVATIVES: AN APPROACH TO PYRAN-CONTAINING NATURAL PRODUCTS

By

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DOCTOR OF PHILOSOPHY

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Dedicated to the memory of my grandmother, Ellen Victoria Bradley.

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TABLE OF CONTENTS

page

ACKNOWLEDGMENTS iii

ABSTRACT vii

CHAPTER

1 INTRODUCTION 1

The [4+3] Cycloaddition Reaction 4
Application of 8-Oxabicyclo[3.2.1]Octene Derivatives in Synthesis 9
The Asymmetric [4+3] Cycloaddition Reaction 12
Olefin Metathesis 30
Mechanism of Activity of Grubbs' Ruthenium-Based Olefin Metathesis Catalysts 33
Types of Olefin Metathesis Reactions 36
Ring-opening metathesis polymerization (ROMP) 36
Ring-closing metathesis (RCM) 38
Cross metathesis (CM) 41
Ring-opening metathesis/cross metathesis (ROM/CM) 47
Domino Ring-Closing Metathesis/Ring-Opening Metathesis (RCM/ROM) 49
Catalytic Asymmetric Olefin Metathesis 61

2 RESULTS/DISCUSSION 73

Intermolecular Ring-Opening Metathesis/Cross Metathesis 73
Domino Ring-Closing Metathesis/Ring-Opening Metathesis (RCM/ROM) 79
Toward Spiro-Fused Bicyclic Systems 79
Toward Linear-Fused Bicyclic Systems 85
Toward Bridged-Fused Bicyclic Systems 95

3 CONCLUSIONS AND FUTURE WORK 98

4 EXPERIMENTAL PROCEDURES 100

APPENDIX SELECTED SPECTRA 144

LIST OF REFERENCES 191

BIOGRAPHICAL SKETCH 197

Abstract of Dissertation Presented to the Graduate School
of the University of Florida in Partial Fulfillment of the
Requirements for the Degree of Doctor of Philosophy

RING-OPENING METATHESIS/CROSS METATHESIS AND DOMINO METATHESES OF 8-OXABICYCLO[3.2.1]OCTENE DERIVATIVES: AN APPROACH TO PYRAN-CONTAINING NATURAL PRODUCTS

By

Lynn C. Usher

August 2003

Chair: Dennis L. Wright
Major Department: Chemistry

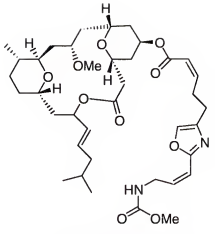
The pyran moiety is common to a wide range of natural products, including the marine macrolides Leucascandrolide A and Latrunculin B. It is present in the former as an independent ring and in the latter as part of a bridged-fused system. A notable feature of the pyrans contained in both molecules is the *cis*-2,6-disubstitution pattern. Traditionally, pyrans have been constructed stereoselectively via aldol-based chemistry. We have developed unique methodology to assemble *cis*-2,6-disubstituted pyrans by ring-opening metathesis/cross metathesis (ROM/CM) of oxabicyclic octene derivatives using Grubbs' ruthenium-based metathesis catalysts. With judicious choice of donor alkenes, the newly generated pyran contains two highly differentiated olefins for further selective functionalization. We have further extended the methodology to include intramolecular RCM/ROM. This was achieved by tethering the donor olefin to the bicyclic ring system such that the second metathesis process prompts ring closure, generating annulated pyrans. The synthesis of three main classes of compounds was targeted. Placement of the tether at C1 led to spiro-fused bicyclic systems. Linear-fused

systems resulted from a tether at C2. Bridged-fused compounds were approached by attachment of the donor olefin at C3. The success of these RCM/ROM processes was highly dependent on the hybridization at C3 of the oxabicyclic octene. Sluggish reactions were accelerated by converting C3 from an sp^2 to an sp^3 center. In the case of the C2-tethered intermediates, the stereochemistry of the tether further influenced the level of success of the RCM/ROM reaction, with *endo*- tethers being more favorably aligned for RCM/ROM. Fused pyrans and tetrahydrofurans were achieved in good-to-excellent yield with careful consideration of the effects of the C3, C2, and C1 substituents.

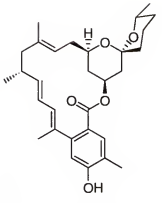
CHAPTER 1
INTRODUCTION

One of the main characteristics of a superior synthetic method is its ability to achieve considerable increase in molecular complexity in a single step from a diverse range of readily available starting materials. It is, of course, also imperative that the method focus on the construction of molecules of some significance, be it in nature or otherwise. The pyran moiety is widely abundant in nature, existing independently or as part of a fused ring in many complex systems (Figure 1-1). Leucascandrolide A[1] (**1**), for example, contains a *cis*-2,6-disubstituted pyran. In milbemycin β3[2-5] (**2**), the pyran is part of a spiro-fused ring system. In forskolin[6] (**3**), it exists as a linear-fused structure, and in the latrunculins[7] (**4**, **5**) as part of a bridged-fused system.

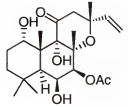
Traditionally, construction of pyrans has relied, for the most part, on aldol-based chemistry, though several novel methods have been reported. One example is Kozmin's synthesis of Leucascandrolide A (**1**) (Scheme 1-1).[8] He constructed the *cis*-2,6-disubstituted pyran via a Prins desymmetrization. The Prins precursor **8** was obtained via a vinylagous transesterification of 4-methoxy-3-butenone (**7**) with heptadienol **6**. Exposure of **8** to trifluoroacetic acid at 5°C followed by basic hydrolysis yielded the *cis*-2,6-disubstituted tetrahydropyran **9**, which was further elaborated to Leucascandrolide A(**1**).



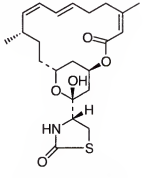
Leucascandrolide A **1**



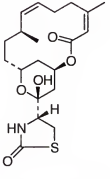
Milbemycin β3 **2**



Forskolin **3**

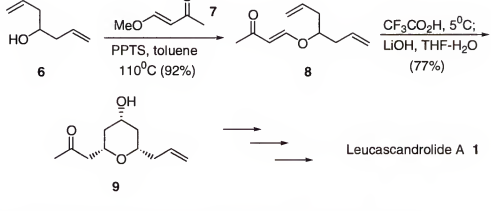


Latrunculin A **4**



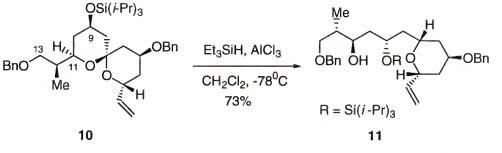
Latrunculin B **5**

Figure 1-1. Natural products containing the cis-2,6-disubstituted pyran moiety



Scheme 1-1. Kozmin's construction of the *cis*-2,6-disubstituted pyran of Leucascandrolide A

Crimmins, in his approach to Leucascandrolide A (**1**), used a highly functionalized spiroketal **10**, synthesized in nine steps from a known pyrone, to incorporate the *cis*-2,6-disubstituted pyran (Scheme 1-2).[9] Exposure of spiroketal **10** to $AlCl_3 - Et_3SiH$ resulted in a chelation-controlled reductive cleavage, affording tetrahydropyran **11** as a single isomer. Crimmins and coworkers explained the selectivity based on bidentate coordination of the C13 benzyl and the C11 spiroketal oxygen to the metal center. Reduction of the oxocarbenium ion, which results from this selective activation of the C11 oxygen-anomeric carbon bond, promotes axial approach of the hydride to give tetrahydropyran **11**.



10 **11**

Scheme 1-2. Crimmins' synthesis of the *cis*-2,6-disubstituted pyran of Leucascandrolide A

An interesting approach to the construction of the pyran moiety relies on specific cleavage of the 8-oxabicyclo[3.2.1]oct-6-en-3-one skeleton **12** at the C6-C7 bond. Bicyclo[3.2.1]octene derivatives **12**, synthesized by a [4+3] cycloaddition reaction between an oxyallyl cation and a cyclic 1,3-diene, have proven to be useful synthons in natural product synthesis owing to their extreme versatility.[10,11] Depending on the diene partner in the [4+3] cycloaddition, a variety of systems can be achieved (Figure 1-2). With furan, oxabicyclic derivatives result, with N-protected pyrrole, aza- systems, and with cyclopentadiene, carbocycles. Adding to the versatility of these molecules, cleavage at varying points on the bicycle lead to a wide range of functionally diverse systems.[12-15]

Opening at the bridgehead yields cycloheptenones **13**. Cleavage at C2-C3 affords 2,5-disubstituted dihydrofurans, dihydropyrroles or cyclopentenes **15**. 2,6-Disubstituted pyran, piperidine and cyclohexane derivatives **14** arise from cleavage of the C6-C7 bond.

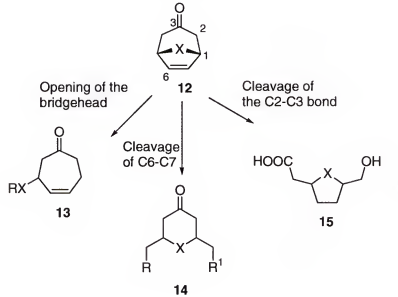


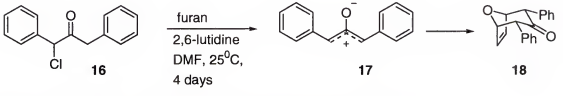
Figure 1-2. Bicyclo[3.2.1]octene derivatives as versatile synthons for natural product synthesis

The usefulness of bicyclic[3.2.1]octenes is attributable not only to their potential for diversity, but also to their ease of preparation. Relevant to this dissertation is the synthesis of 8-oxabicyclo[3.2.1]oct-6-en-3-one. In the interest of completeness, a brief history of the [4+3] cycloaddition follows, with an emphasis on reactions with furan.

The [4+3] Cycloaddition Reaction

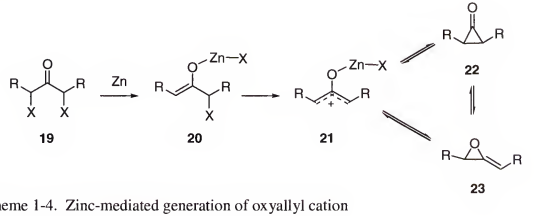
The [4+3] cycloaddition of the furan nucleus to oxyallyl cations to produce oxabicyclic[3.2.1]octene derivatives has revolutionized the construction of bicyclic ring systems and has increased their value as building blocks in natural product synthesis. The reaction, which can be viewed as a [4π(4C)+2π(3C)] combination, with the oxyallyl cation acting as the 2π component, was first discovered by Fort. He observed that

treatment of α-chlorodibenzyl ketone **16** with 2,6-lutidine in the presence of furan with DMF as a solvent at 25°C for four days yielded cycloadduct **18** (Scheme 1-3). Further studies led to the proposal of the intermediacy of the oxyallyl cation **17**, and its reaction with a series of 1,3 dienes, both cyclic and acyclic, has been extensively reviewed.[10,11,16-19]



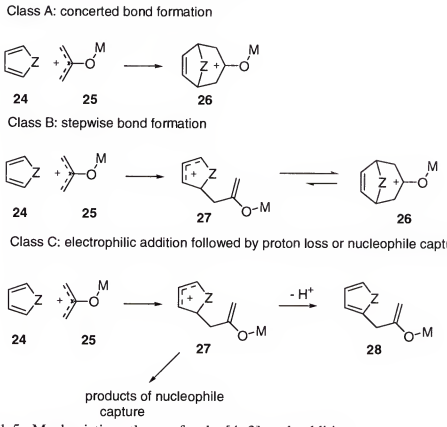
Scheme 1-3. The [4+3] cycloaddition of furan to α-chlorodibenzylketone

In 1973, Hoffmann first reviewed the chemistry of the oxyallyl cation.[20] He demonstrated that oxyallyl cations are generated from α,α′-dihaloketones **19** via a zinc-mediated two-electron reduction (Scheme 1-4). Loss of the allylic halogen by an S_N1-type ionization of the resulting metal enolate **20** yields oxyallyl cation **21**, which can interconvert between the cyclopropanone and the allene oxide structural isomers **22** and **23** respectively.



Scheme 1-4. Zinc-mediated generation of oxyallyl cation

Based on extensive mechanistic studies, Hoffmann rationalized that the [4+3] cycloaddition reaction could proceed either by a concerted bond formation or by a stepwise process to generate the desired 7-membered ring systems. In cases where electrophilic addition is followed by proton loss or nucleophilic capture, ring formation fails to occur and substitution products dominate (Scheme 1-5).



Scheme 1-5. Mechanistic pathways for the [4+3] cycloaddition

Several factors play a role in determining the stereochemistry of the reaction. The electrophilicity of the allyl cation intermediate, the nucleophilicity of the diene and the polarity of the solvent all influence the stereochemical outcome. The two proposed transition states for the [4+3] cycloaddition reaction are an extended chairlike formation and a compact, boat-like arrangement (Figure 1-3). The situation becomes more complex when acyclic cations are employed since these can exist in one of three forms: the "U"

form, the sickle form or the most commonly observed "W" configuration. Various studies have illustrated the ability to control the steric course of the reaction with judicious choice of reagents and reaction conditions.

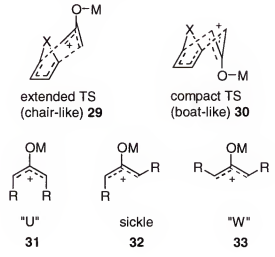
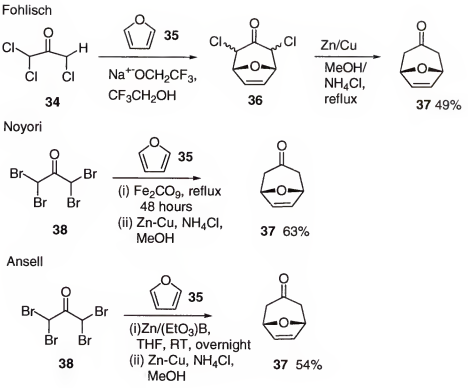


Figure 1-3. Possible transition states and oxyallyl cation configurations in the [4+3] cycloaddition reaction

Since Hoffmann's first application of zinc-mediated reduction, several other methods for generating oxyallyl cations have been reported. These involve variations of Hoffmann's reductive conditions, as well as new approaches requiring the use of base, Lewis acids and light. Use of Cu/NaI produces oxyallyl cations, which proceed via a concerted, compact transition state. The ionic nature of the Na-O bond of the oxyallyl cation accounts for its low electrophilicity and its preferred transition state along the reaction pathway. Oxyallyl cations generated using Zn/Cu or Zn/Ag couples or $Zn/(EtO)_3B$ are intermediate in electrophilicity, and the stereochemistry of the cycloadducts indicates the interference of a stepwise mechanism of addition. Noyori's conditions, entailing the use of diiron nonacarbonyl (Fe_2CO_9), generate the most electrophilic oxyallyl cation. These conditions lead to improved cycloaddition reactions

with poorly nucleophilic dienes due to the increased electrophilicity of the highly covalent iron-oxygen bond. The stereochemistry of the products indicates the dominance of a stepwise mechanism.

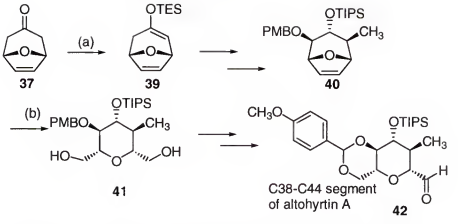
A second means of generating oxyallyl cations requires exposure of α-haloketones to basic conditions. Several groups have studied this particular method, but one of the major contributions was made by Fohlisch et al. who showed that chloro-substituted 8-oxabicyclo[3.2.1]oct-6-en-3-ones could be synthesized from furans and trichloro-, tetrachloro- or pentachloroacetones in methanol, 2,2,2-trifluoroethanol or 2,2,3,3-tetrafluoroethanol in the presence of the corresponding sodium alkoxides. Subsequent reduction with activated zinc yields 8-oxabicyclo[3.2.1]oct-6-en-3-one. Other basic conditions that have seen some success are silver tetrafluoroborate/triethylamine, silver oxide, and lithium perchlorate/triethylamine. Several large-scale preparations of 8-oxabicyclo[3.2.1]oct-6-en-3-one have illustrated its utility as a synthetic starting material (Scheme 1-6).[21-23] Generation of oxyallyl cations from α-halosilylenol ethers by Lewis acid-promoted heterolysis or by irradiation of dienones in the presence of furan have been investigated but their use is not widespread.



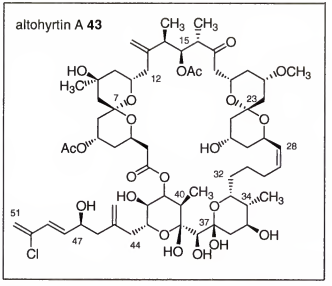
Scheme 1-6. Multigram scale syntheses of 8-oxabicyclo[3.2.1]oct-6-en-3-one

Application of 8-Oxabicyclo[3.2.1]Octene Derivatives in Synthesis

Hoffmann has proven the synthetic utility of oxabicyclic octene derivatives, 8-oxabicyclo[3.2.1]oct-6-en-3-one in particular, using them as the starting point in his approach to several pyran-containing natural products . The *cis*-2,6-disubstituted pyran in altohyrtin A **43** was achieved by ozonolysis of the C6-C7 bond of **40** (Scheme 1-7).[24] Enantioselectivity was attained in the first transformation of the oxabicyclo[3.2.1]octene **38** by deprotonation with a chiral lithium amide base. The resulting enolate was trapped with triethylsilyl chloride to obtain the chiral silylenol ether **39**, which was further functionalized to yield the ozonolysis precursor **40**.



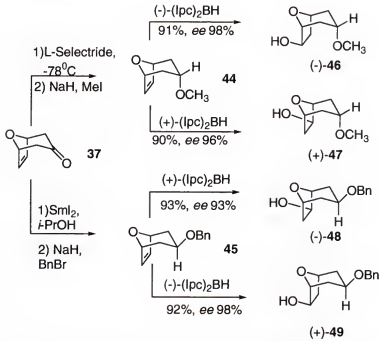
a)(i) LiCl, (+)-bis[(*R*)-1-phenylethyl]amine, THF, -78^{0}C, (ii) *n*-BuLi, ***meso*-1**, THF, -115^{0}C, (iii) TESCl, NEt_3, -78^{0}C (95%); (b) (i) O_3, CH_2Cl_2/MeOH, -95^{0}C, (ii) $NaBH_4$ (94%)



Scheme 1-7. Hoffmann's approach to altohyrtin A from 8-oxabicyclo[3.2.1]oct-6-en-3-one (**37**)

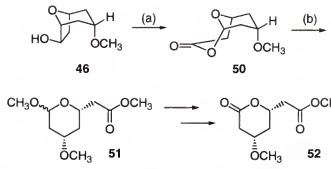
In recent years, Hoffmann et al. have disclosed several strategies for the synthesis of phorboxazole A (**57a**), bryostatin 1, and the mevinic acids, compactin (**53a**), mevinolin (**53b**) and pravastatin (**53c**).[13] These are all based on oxidative opening of the C6-C7 bond of oxabicyclo[3.2.1]octenes (Scheme 1-8). The sequence involves reduction and protection of the bicyclic ketone **37** to yield both *endo*- and *exo*- ethers **44** and **45**

respectively. Asymmetric hydroboration desymmetrizes the ethers to yield all four stereoisomeric alcohols **46-49**.

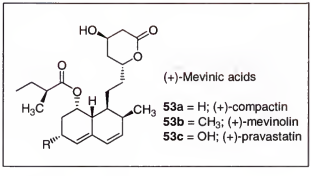


Scheme 1-8. Hoffmann's application of oxabicyclo[3.2.1]octenes to natural products

PCC oxidation followed by Baeyer-Villiger oxidation prepares the system for oxidative cleavage by acidic methanolysis to give the 2,6-disubstituted pyran methoxyacetals **51** (Scheme 1-9). Conversion to the hemiacetals and subsequent oxidation generates lactone **52**, relevant to the synthesis of rings B, C, and D of spongistatin and to the lactone moiety of the mevinic acids (**53a-c**). In the approach to the phorboxazoles, methoxyacetal **54** was converted to the *trans*-2,6-disubstituted pyran **55** upon treatment with allyltrimethylsilane in the presence of trimethylsilyltriflate in acetonitrile (Scheme 1-10).[14] This was further elaborated to complete the C3-C13 segment **56** of the phorboxazoles.



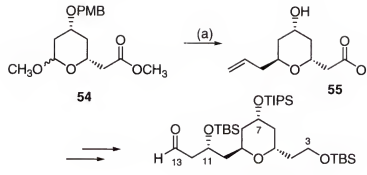
a)(i) PCC/SiO_2 (97%); (ii) *m*-CPBA, $NaHCO_3$ (87%); b) CH_3OH, H^+ (86%)



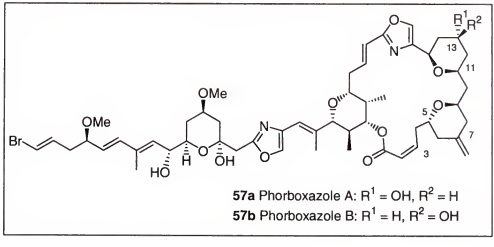
Scheme 1-9. Toward the synthesis of the mevinic acids

The Asymmetric [4+3] Cycloaddition Reaction

In the previous examples, asymmetry was achieved by desymmetrization of the bicyclic octene with chiral reagents. To improve the synthetic utility of the [4+3] cycloaddition, several groups have recently begun to address the issue of achieving enantioselectivity in the reaction, taking one of two basic approaches. The first entails the use of chiral dienes and the second the use of chiral allyl or oxyallyl cations. The idea of using chiral dienes as a means of stereoinduction in this reaction was first introduced by Hoffmann and coworkers in 1988.[25]



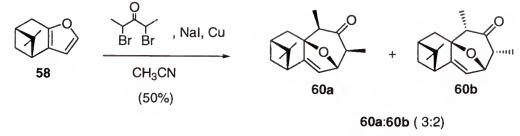
a) allyltrimethylsilane, TMSOTf, CH_3CN, -20^{0}C to r.t., 1h (85%, >99% de



Scheme 1-10. Toward the synthesis of the phorboxazoles

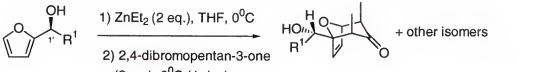
These researchers utilized pinofuran **58** to accomplish a diastereoselective [4+3] cycloaddition (Scheme 1-11). They demonstrated that treatment of α, α′-dibromoketone **59** with NaI/Cu in the presence of pinofuran (**58**) yielded 50% of stereoisomeric cycloadducts **60a** and **60b** in a ratio of 3:2 respectively. The cycloaddition was π-facially selective with the major cycloadduct resulting from attack at the face *anti* to the *gem*-dimethyl bridge. Hoffmann explained the *cis*-selectivity with respect to the C2and C4 methyl groups in terms of an *anti-cis*-extended transition state, citing steric repulsion from the pinene skeleton as unfavorable in the compact transition state. Although

Hoffmann demonstrated the possibility for controlling stereoselectivity of the [4+3] cycloaddition, overall yield of the expected cycloadduct as well as diastereomeric excess were relatively low.



Scheme 1-11. Hoffmann's stereoselective cycloaddition to pinofuran

Several years later in 1996, Lautens et al. reported on the use of chiral furfural-derived dienes to induce asymmetry.[26] Using Noyori's diiron nonacarbonyl conditions, they studied the cycloaddition of 2,4-dibromopentan-3-one with a range of chiral furyl alcohols and ethers, varying the steric bulk at the C2′ position (Scheme 1-12).



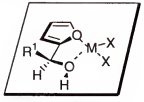
61a R^1 = t-Bu
61b R^1 = c-hexyl

62a R^1 = t-Bu (70-80%) *de* (96:4)
62b R^1 = c-hexyl (60-80%) *de* (95:5)

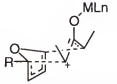
Scheme 1-12. Lautens' approach to enantiomerically pure [4+3] cycloadducts

Lautens and coworkers proposed that a metal ion such as zinc or magnesium would enhance diastereoselectivity through chelation with the furan and side-chain oxygens (Figure 1-4). They demonstrated that "chelation-controlled" products formed only in the presence of the free alcohol at C1′. Diastereoselectivity was not significantly altered when additional oxygens were placed at the C2′ position, indicating that the

stereoselectivity of addition was controlled predominantly by the furyl oxygen. Another interesting observation was that formation of magnesium or zinc alkoxides by deprotonation of the free alcohol with the corresponding divalent organometallic reagent led to cycloadducts that placed the C2 and C4 methyl groups in a diaxial orientation (Figure 1-4). Under optimized conditions (2 equivalents each of diethyl zinc and 2,4-dibromopentan-3-one in THF) yields as high as 80% and good diastereomeric excess (>90%) were determined.



diastereofacial selectivity



proposed extended transition state model

Figure 1-4. Control of diastereoselectivity in the [4+3] cycloaddition

An extensive study was performed by Montaña et al. to investigate the effect of the choice of chiral diene on the *cis*/*trans*, *endo*/*exo*, and π-facial selectivity of the [4+3] cycloaddition reaction.[27] They synthesized a series of C2-functionalized furans using chiral auxiliaries to establish chirality and taking into account three major criteria that might influence the π-facial stereoselectivity of the reaction (Figure 1-5). First, the distance between the closest stereocenter of the chiral auxiliary and the reactive C2 carbon of furan was varied from one to two to three bonds. Furthermore, the volume and shape of the auxiliary as well as the identity of the linker connecting it to the furan were modified. Carbonate, ester, thioether, sulfoxide and cycloalkyl linkers were examined.

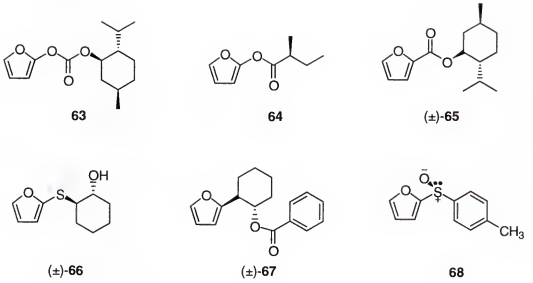
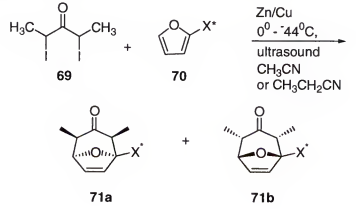


Figure 1-5. Some chiral furan derivatives studied by Montaña et al.

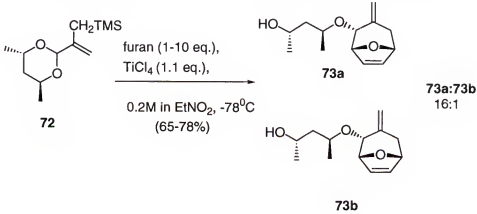
Montaña and coworkers utilized a modified version of Hoffmann's conditions for the [4+3] cycloaddition.[28] Zn/Cu couple was used to generate the oxyallyl cation intermediate from α,α′-diiodo- or dibromoketones, allowing for the possibility of *cis/trans* isomers at the methyl substituents on the resulting bicycle (Scheme 1-13). The reaction was carried out at low temperature (0°C to ¯44°C) under sonochemical conditions, resulting in reduced reaction times and increased stereoselectivity.



Scheme 1-13. Modified [4+3] cycloaddition reaction of chiral furans

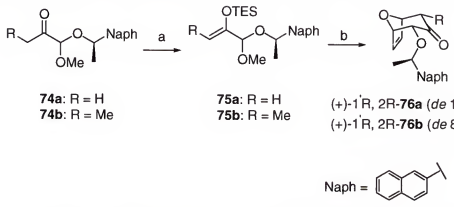
In the series of dienes studied, complete *cis/trans* and *endo/exo* diastereoselectivity was achieved. Poor facial diastereoselectivity was observed with auxiliaries containing the stereocenter more than two bonds away. Although increased selectivities were seen in cases where the stereocenter was only one or two bonds removed from the reactive center, the volume and shape of the auxiliary influenced the selectivity. The best results were obtained with the *p*-tolyl sulfinyl substituted furan **68**, with a diastereomeric excess of 54% being determined.

The other alternative to achieving asymmetry in the [4+3] cycloaddition reaction applies chirality, not to the diene, but to the second component of the reaction, the allyl cation. Several methods to generate such species chirally have been reported in recent years. In 1997, Harmata et al. introduced the idea of using chiral (timethylsilyl)methyl allylic acetals to generate heteroatom-stabilized chiral allylic cations (Scheme 1-14).[29,30] Reaction of acetal **72** with furan in nitroethane in the presence of titanium tetrachloride yielded 65-70% of a 16:1 mixture of cycloadducts **73a** and **73b**. The source of diastereoselectivity was unclear. Despite variations in Lewis acid, number of equivalents of furan and concentration of chiral acetal, the major cycloadduct was always the same.



Scheme 1-14. Chiral allylic acetals as asymmetric allylic cations in [4+3] cycloadditions

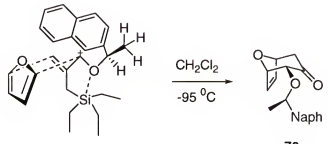
A similar approach by Hoffmann involved the use of a Lewis acid-mediated [4+3] cycloaddition (Scheme 1-15).[31,32] Hoffmann et al. designed acyclic, chiral α-ketoacetals **74a** and **74b**, employing enantiopure 1-phenyl ethanol and 1-(2-naphthyl) ethanol to introduce chirality. Formation of the corresponding chiral triethylsilyl enol ethers **75a** and **75b** and subsequent reaction with furan in dichloromethane at -95°C led to cycloadducts **76a** and **76b** in yields as high as 91% and *de's* ranging from 82-100%.



Scheme 1-15. Hoffmann's approach to diastereoselective [4+3] cycloaddition

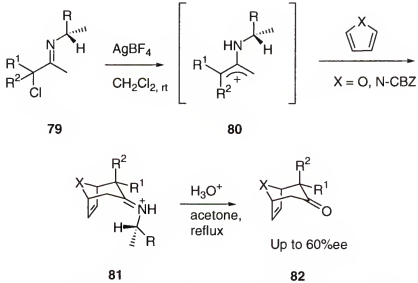
Hoffmann and coworkers proposed a type of silicon-oxygen chelation to account for the observed diastereoselectivity (Scheme 1-16). They observed that solvents with donor oxygen sites such as ether, tetrahydrofuran and nitroethane effected decreases in stereoselection. The fact that the alkyl substituent at C1 of the chiral auxiliary had little effect on the diastereoselectivity led the researchers to believe that this group is not in close proximity to the reactive centers. As the nature of the aromatic moiety was found to be significant, with an increase in stereoinduction being observed from phenyl to 2-naphthyl, Hoffmann et al. proposed that this group blocked one of the π faces of the allyl

cation in the favored transition state. 2-Naphthyl was more effective in this capacity than phenyl.



Scheme 1-16. Hoffmann's model for the asymmetric [4+3] cycloaddition

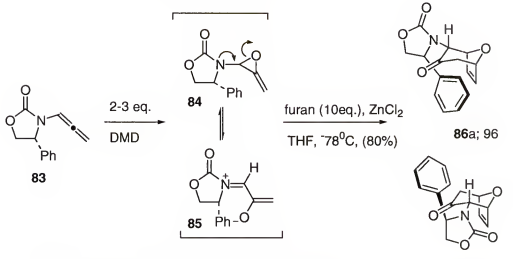
In 1997, Kende's laboratory reported a novel approach to chiral allylic cations, involving the use of (S)-1-phenylethylamine derived α-chloroimines **79** (Scheme 1-17).[33] They demonstrated that the chiral, 2-aminoallyl cations **80**, obtained from the starting α-chloroimines, underwent π- facial and *endo* selective [4+3] cycloaddition with furan or N-protected pyrrole to yield intermediate iminium salts **81**. Mild hydrolysis of the chiral auxiliary afforded the bicyclo[3.2.1]octenes **82**.



Scheme 1-17. Asymmetric [4+3] cycloadditions from chiral α-chloroimines

Yields obtained in the cycloaddition were moderate to poor and the highest enantiomeric excess observed was 60%. Though no confirmed explanation of the π-facial stereoselectivity was reported, Kende et al. proposed the possibility of preferential attack at the less hindered face.

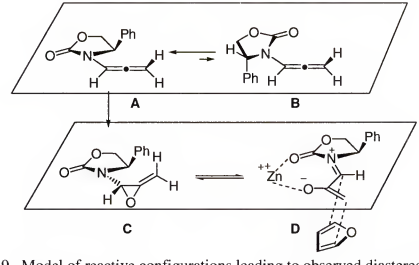
Another approach to chiral oxyallyl cations was reported by Hsung et al. in 2001.[34,35] Epoxidation of allenamides **83** led to chiral allene oxides **84** and **85**, masked nitrogen-stabilized oxyallyl cations (Scheme 1-18).



Scheme 1-18. Hsung's chiral allene oxide approach to an asymmetric [4+3] cycloaddition

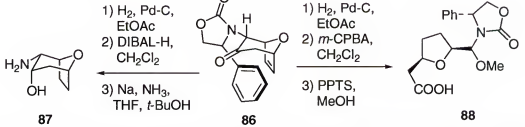
Hsung and coworkers observed one-pot epoxidation/[4+3] cycloaddition sequences in which the epoxidized allenamide reacted with both furan and cyclopentadiene to generate cycloadducts **86a** and **86b** in yields ranging from 40-80%. High diastereoselectivities (≥95:5) were observed for allenamides containing phenyl and dibenzyl groups α- to the nitrogen, yet the presence of benzyl groups in that position resulted in a drastic fall in diastereoselectivity. The researchers offered a preliminary model to explain the diastereoselectivity of the reaction (Scheme 1-19). Conformation A, due to the

minimized dipole interaction, should be favored. If epoxidation occured on the less hindered face, away from the bulky phenyl group, allene oxide C and subsequently oxyallyl intermediate D would be expected. Furan or cyclopentadiene would then approach from the less hindered face, opposite the phenyl group.



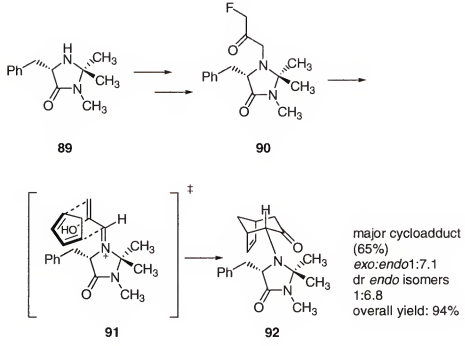
Scheme 1-19. Model of reactive configurations leading to observed diastereofacial selectivity

The challenge of this approach is the removal of the chiral auxiliary. Hsung et al. offered two solutions. Hydrogenation, DIBAL-H reduction, then Birch-type reduction of the cycloadduct led to the amino alcohol **87** (Scheme 1-20). Alternatively, hydrogenation, Baeyer-Villiger oxidation then methanolysis gave chiral aminal **88** as a single isomer. These methods, however, either diminish the versatility of the oxabicyclic octene or destroy the bicycle completely.



Scheme 1-20. Cleavage of the chiral auxiliary after the [4+3] cycloaddition with chiral allenamides

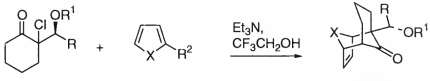
In 2001, Myers and coworkers reported a [4+3] cycloaddition using a chiral α-amino α′-fluorooxyvinyliminium ion **91** derived from chiral amine **89** (Scheme 1-21).[36] In the presence of triethylamine and hexafluoro-2-propanol as a solvent, the α-amino α′-fluoroketone **90** reacted with cyclopentadiene at room temperature, generating a mixture of four diastereomeric cycloaddition products **92** in 94% yield. The ratio of *endo* to *exo* products was 7.1:1 and the diastereomeric ratio of *endo* isomers was 1:6.8.



Scheme 1-21. The [4+3] cycloaddition using chiral α-amino α′-fluorooxyvinyliminium ions

In 1999, Cha et al. developed an asymmetric approach to the [4+3] cycloaddition reaction based on the directing ability of allylic alkoxy substituents.[37] Their work focused on the generation of cyclic oxyallyl cations from chiral α-haloketones under Föhlisch conditions (Scheme 1-22). Both the protected β-alkoxy functionality and the free alcohol were examined. When the secondary alcohol was protected as its silyl ether, cycloaddition afforded only cycloadduct **95**. Yields were moderate to high with

unsubstituted furan as the diene partner in the cycloaddition ranging from 48% with bulky R groups to 81% with a methyl group in position R. With cyclopentadiene, moderate yields (52-57%) were obtained in most cases. Very low yields (25%) of cycloadduct **95** were observed with 2,5-dimethyl furan.



93

94a = O, R^2 = H
94b = CH_2, R^2 = H
94c = O, R^2 = Me

95a = O
95b = CH_2

Scheme 1-22. Directing ability of allyl alkoxy groups in the asymmetric [4+3] cycloaddition

Cha and coworkers proposed a model explaining approach of the diene from the less-hindered face of the oxyallyl cation, that is, the face opposite the bulky R group in conformation A (Figure 1-6). The major cycloadduct **95** also supported a preference for the "compact" transition state in the cycloaddition. The low yields observed with 2,5-dimethyl furan may be due to steric crowding caused by the methyl groups in the transition state as shown in conformation A.

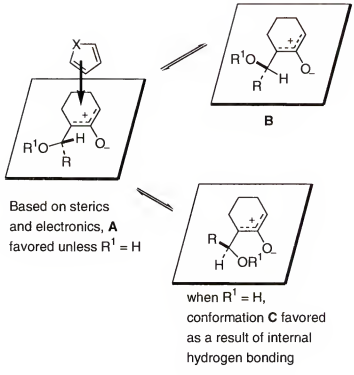
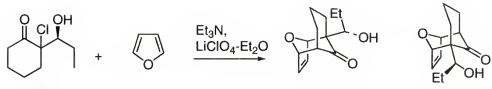


Figure 1-6. Diastereofacial preference in Cha's asymmetric [4+3] cycloaddition

On the contrary, the products resulting from cycloaddition reactions involving the free alcohol reflected a difference in the directing effect of the free hydroxyl versus the ethers. In this case a mixture of isomers was observed, the major, opposite in stereochemistry from that observed with the protected alcohols, resulting from conformation C (Scheme 1-23). This observation indicated the involvement of hydrogen bonding in the transition state. Though the yield of the reaction was modest (48%) and the diastereoselectivity only 1:3 in favor of **95b**, replacement of trifluoroethanol by 5M lithium perchlorate/ether triggered an increase in diastereoselectivity to greater than 15:1 (**95b**:**95a**). Yields increased to 60-65%.

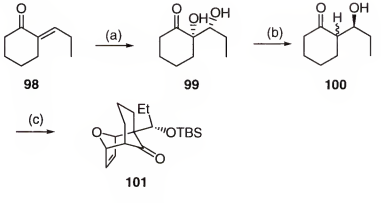


96 **97a** **97b**

<1 : 15

Scheme 1-23. Directing ability of allyl hydroxy groups in the asymmetric [4+3] cycloaddition

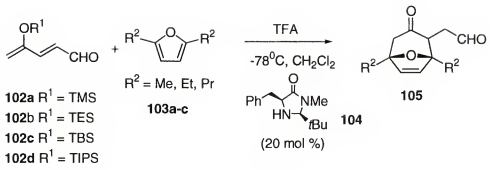
Cha approached enantiomerically enriched alcohols via the Sharpless asymmetric dihydroxylation of *E*-olefin **98** (Scheme 1-24). Enantiomeric excess of cycloadducts so derived exceeded 90%.



a)OsO_4, $(DHQD)_2$-PHAL; b) (i) MsCl; (ii) NaOMe; (iii) SmI_2;
c) (i) TBSOTf; (ii) SO_2Cl2; (iii) furan, Et_3N, CF_3CH_2OH; (*ee* >90%)

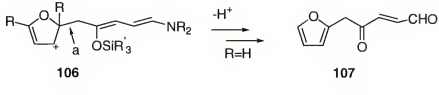
Scheme 1-24. Synthesis of enantiomerically enriched cycloadducts via optically active cyclic oxyallyl cations

In 2003, Harmata et al. raised the issue of organocatalysis in the asymmetric [4+3] cycloaddition, proposing the formation of a chiral iminium ion derived from silyloxy pentadienals **102a-d** in the presence of catalytic amounts of a known chiral imine **104** (Scheme 1-25).[38]



Scheme 1-25. Asymmetric organocatalysis of [4+3] cycloaddition

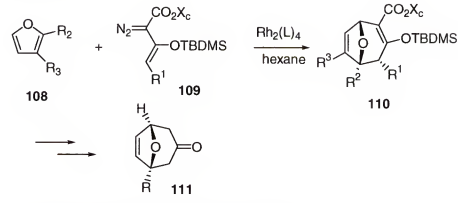
They observed low yields and poor *ee's* in reactions involving furan; however, when 2,5-disubstituted furans were used, yields as high as 64% were obtained. The reactions were *endo* selective and *ee's* of 81-90% were determined. Harmata et al. attributed the poor yields and *ee's* seen with furan to formation of intermediate **106** in a stepwise cycloaddition (Scheme 1-26). In its most stable conformation, ring closure would be disfavored, yet substitution could occur readily, accounting for the formation of alkylation product **107**. Attempts to react more highly substituted dienophiles were unsuccessful. Though yields were relatively high, enantiomeric excess was less than 10%.



Scheme 1-26. Stepwise cycloaddition possibly leads to substitution product

Davies et al. have reported an asymmetric [4+3] annulation involving a rhodium-stabilized vinyl carbenoid addition to furan (Scheme 1-27).[39] Asymmetry was approached via chiral auxiliaries on the vinyl carbenoid precursor **109** in conjunction with chiral rhodium catalysts. A 2-silyloxy-substituted vinylcarbenoid underwent a tandem

cyclopropanation/Cope rearrangement with furan to yield oxabicyclic[3.2.1]octanes **110** (Scheme 1-27). These were readily converted to enantiomerically enriched 8-oxabicyclo [3.2.1]octenones **111**.

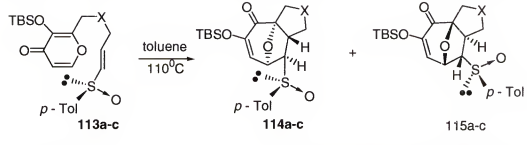


Scheme 1-27. Rhodium(II) carboxylate decomposition of chiral vinyldiazomethanes in the presence of furan

Davies and coworkers demonstrated that the use of chiral auxiliaries tethered to the carbenoid by an ester linker promoted the highest levels of asymmetric induction (82-95% *de*). The products could be purified by chromatography to greater than 99% *de*. (*S*)-lactate and (*R*)-pantolactone auxiliaries were shown to promote opposite absolute stereochemistry in the cycloaddition. An interaction between the carbonyl group of the auxiliary and the carbenoid offers an explanation for the level of asymmetric induction (Figure 1-7).

Figure 1-7. Interaction between carbonyl group of auxiliary and the carbenoid

An interesting alternative to the [4+3] cycloaddition to access enantiopure oxabicyclic derivatives is the thermal [5+2] intramolecular cycloaddition of β-silyloxy-γ-pyrones to alkenes substituted with chiral sulfoxides and sulfimines. In 2000, Mascareñas et al. performed a detailed study of this reaction, addressing issues of regio- as well as stereoselectivity.[40,41] They reported that placement of a *p*-tolylsulfinyl chiral auxiliary at the *trans*-terminal position of alkene precursors of type **113a-c** resulted in high yields of cycloadduct with high diastereomeric excess (91:9 to 97:3) (Scheme 1-28).



113a-c **114a-c** 115a-c

X = $C(CN)_2$
X = $C(CO_2Et)_2$
X = S

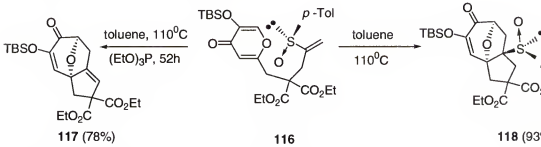
X = $C(CN)_2$; 98%, **114a**:**115a** (91:9)
X = $C(CO_2Et)_2$; 99%, **114b**:**115b** (97:3)
X = S; 95%, **114c**:**115c** (93:7)

Scheme 1-28. Intramolecular [5+2] annulation of optically enriched pyones with alkenylslfoxide tethers

Mascareñas and coworkers explained the facial selectivity as arising from the *S-trans*-type configuration adopted by the alkenylsulfoxide unit in the transition state to avoid repulsive dipole-dipole interactions with the pyrone (Figure 1-8). Approach from the less hindered face is favored.

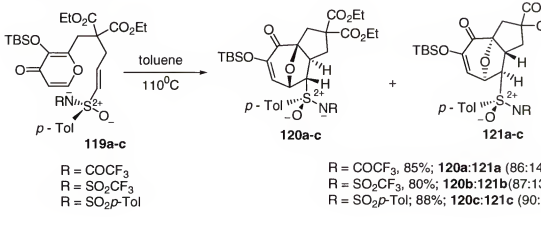
The regioisomeric adducts were similarly obtained (Scheme 1-29). It was, however, necessary to place the sulfoxide unit at the internal position of the alkene rather than the terminal one. This configurational adjustment resulted not only in an increased yield of more than 40%, but also the formation of cycloadduct **118** as a single

diastereomer. In this case, presumably, the alkenylsulfoxide favors an *S-cis*-conformation when approaching the pyrone, perhaps to avoid negative interactions with the *tert*-butylsilyloxy group (Figure 1-8).



Scheme 1-29. The [5+2] annulation to yield regioisomeric products

To obtain the enantiomeric series of cycloadducts, Mascareñas et al. discovered that replacement of the sulfoxide with an *N*-protected sulfoximine inverted the diastereofacial selectivity observed with the sulfoxide derivatives (Scheme 1-30). They proposed that preference for an *S-trans* arrangement of the nitrogen substituent relative to the alkene was responsible for the difference in facial selectivity (Figure 1-8). In all cases, cleavage of the chiral auxiliary was achieved by the action of Raney nickel in refluxing toluene.



Scheme 1-30. Intramolecular thermal [5+2] annulation of N-substituted sulfonimidoyl precursors

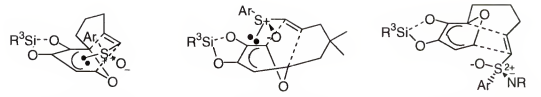


Figure 1-8. Transition states for the thermal [5+2] annulation reaction

Though much room for optimization exists in the current methods, the recent progress toward establishing a general, efficient protocol for the asymmetric [4+3] cycloaddition further highlights the value of oxabicyclic[3.2.1]octenes, as it offers one avenue for achieving enantioselectivity early in the synthetic route.

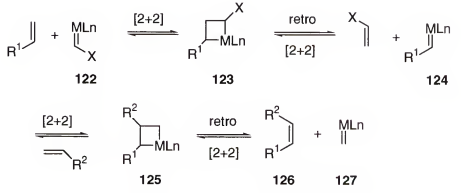
Hoffmann and others have taken advantage of the versatility of these systems, using them as starting points to approach various substructures, common in nature. This dissertation focuses on the use of olefin metathesis of the C6-C7 bond of 8-oxabicyclo[3.2.1]oct-6-en-3-one to accomplish a *cis*-2,6-disubstituted pyrone skeleton with two differentiated, highly functionalizable handles.

Olefin Metathesis

Olefin metathesis has come a long way in terms of its synthetic value since its initial discovery in the mid-1950s. More than a decade after the observation of "double bond-scrambling" reactions, Calderon and coworkers coined the term "olefin metathesis" to describe the metal-catalyzed redistribution of carbon-carbon double bonds.[42,43] Initially, the applicability of this important reaction was curtailed by the absence of well-defined catalyst systems. Until the early 1980s, catalysts consisted of a combination of transition metal salts and main group alkylating agents. The most common ones included

WCl_6/Bu_4Sn, $WOCl_4/EtAlCl_2$, MoO_3/SiO_2 and Re_2O_7/Al_2O_3. Despite their low cost and simple preparation, these catalysts had limited scope for several reasons. First of all, they required harsh conditions and strong Lewis acids that made them intolerant of most functional groups, rendering them useless in late stage synthetic operations. The catalysts were also rather difficult to initiate and control, as very little active species formed in the catalyst mixture.

In the early seventies Chauvin's mechanism for the olefin metathesis reaction led scientists to the development of single-component, homogenous catalysts in the late 1970s and early 1980s, providing them with some basis for catalyst design and a preliminary understanding of catalyst activity. Chauvin proposed a [2+2] cycloaddition of an olefin to a metal alkylidene **122** to generate a metallocyclobutane intermediate **123** that underwent a cycloreversion to yield a new carbon-carbon double bond **126** and metal alkylidene (Scheme 1-31).[44]



Scheme 1-31. Chauvin's mechanism for the olefin metathesis reaction

The evolution of homogenous catalysts led to molybdenum and tungsten alkylidenes **128**, $Mo(CHCMe_2Ph)(N\text{-}2,6\text{-}i\text{-}Pr_2C_6H_3)[OCMe(CF_3)_2]$, and **129**, W(N-2,6-*I*-

$Pr_2C_6H_3$)(CH-*t*-Bu)[OCMe(CF_3)$_2$], the first systems to achieve widespread use particularly in the ring-opening metathesis polymerization (ROMP) reaction of low strain cyclic monomers (Figure 1-9).[45,46] Though these catalysts were highly reactive, they were again limited both by their extreme sensitivity to oxygen and moisture and by their poor functional group tolerance. The development of catalysts incorporating the less oxophilic ruthenium that reacted preferentially with olefins in the presence of alcohols, amides, aldehydes and carboxylic acids overcame many of the aforementioned problems.

After a great many trials with a variety of ruthenium-based catalysts, the discovery of catalyst **130**, (PCy_3)$_2$$Cl_2$Ru=$CHCH_2Ph_2$[47] and then shortly after, **131**, (PCy_3)$_2$$Cl_2$Ru=CHPh[48] led to an explosion in olefin metathesis chemistry in organic laboratories worldwide (Figure 1-9). In 1999, the addition of the highly active ruthenium catalyst **132**, containg an N-heterocyclic carbene ligand, further expanded the scope of the metathesis reaction

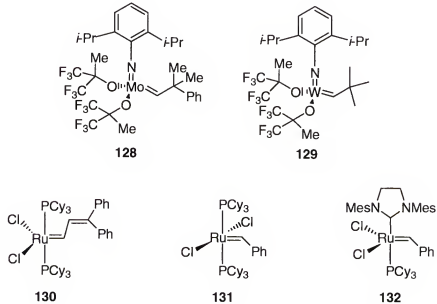
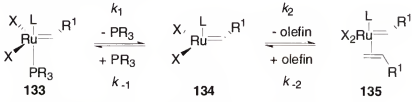


Figure 1-9. Some well-defined olefin metathesis catalysts

Mechanism of Activity of Grubbs' Ruthenium-Based Olefin Metathesis Catalysts

In early mechanistic studies of catalysts of general formula $(PR_3)_2X_2Ru{=}CHR$ it was determined that phosphine dissociation is a crucial, first step in the olefin metathesis pathway (Scheme 1-32).[49] The 16-electron catalyst **133** loses a phosphine ligand, generating an active 14-electron complex **134** that then associates with an olefin substrate, entering the catalytic cycle.



Scheme 1-32. Olefin metathesis occurs by a dissociative pathway

Researchers demonstrated that catalysts displaying the highest activity contained sterically bulky and electron-donating phosphine ligands. Based on these studies, it was proposed that the increase in activity was directly related to the increased rate of dissociation of phosphine. The larger, more basic phosphine ligands, exhibiting a greater *trans*-effect, apparently accelerated dissociation of the second PR_3 ligand and stabilized the Ru(IV) metallocyclobutane intermediate. With these results in hand, Grubbs et al. designed a new series of N-heterocyclic carbene ligands that were larger and more electron-donating than trialkylphosphines. As expected, these catalysts were significantly more active than catalyst **131** and its analogues.

The high activity of **132** and its analogues, however, is accounted for not by increased ability to promote phosphine dissociation, as this critical step is much faster in catalyst **131**, but rather to the relative ease of olefin binding to the 14-electron complex thus formed.[50,51] In the case of catalyst **131**, although phosphine dissociation is faster, the

recoordination of free phosphine competes with binding of the alkene. As a result, the number of catalytic turnovers by the active species is few, as it is readily trapped by free phosphine and returned to the dormant state.

In 2001, Grubbs and coworkers reported extensive studies on the mechanism and activity of ruthenium-based catalysts.[50,51] They demonstrated that all the ligands, L-type, phosphine, halide and carbene, directly affect the relative rates of particular steps along the reaction coordinate. Substitution of phosphine by an N-heterocyclic carbene ligand resulted in a dramatic increase in catalyst activity, but an equally significant decrease in rate of initiation of catalyst by phosphine dissociation. The enhanced activity is due to the increased selectivity for binding alkene substrates as compared to phosphine. The highly electron-donating NHC ligand is thought to better promote and stabilize metal-to-olefin back bonding, stabilizing the 14-electron complex. It is also possible that it accelerates oxidative addition required for formation of the metallocyclobutane. Although it is unclear exactly why rates of catalyst initiation decrease, it is believed that despite the similarity in overall size, the distribution of steric bulk at the ruthenium center may, in the case of catalyst **131**, lead to destabilizing interactions, accelerating loss of phosphine. In catalyst **132**, on the other hand, the interactions may actually stabilize the complex, increasing the energy required for phosphine dissociation.

Grubbs et al. determined that judicious choice of the second phosphine ligand could result in increased initiation and catalyst activity. Replacement of PCy_3 by PPh_3 resulted in a catalyst that promoted polymerization of cyclooctadiene fifty times faster than the PCy_3 complex. The catalyst efficiency can also be improved by choice of halide ligand. The rate of initiation was dramatically enhanced when the X ligand is changed from

chloride to bromide to iodide. This is predominantly due to the increased steric bulk of the larger halide that crowds the ruthenium center, promoting phosphine dissociation. Finally, the catalyst can be tuned based on the choice of the carbene ligand. Once again, steric bulk and electron donating capabilities are the two properties most desired in the R group since they promote loss of phosphine. Since the R substituent can change throughout the olefin metathesis catalytic cycle, its identity is rather significant. Grubbs et al. showed that the methylidene complexes $(PCy_3)_2Cl_2Ru{=}CH_2$ (**136**) and $(IHMes)(PCy_3)Cl_2Ru{=}CH_2$ (**137**) are extremely poor initiators for olefin metathesis at room temperature. Although these are both active in their phosphine free forms, once they are trapped by free PR_3, they become dormant and do not readily re-enter the catalytic cycle.

The major advantage of improved initiation rates is that less catalyst is needed in the reaction since most of the catalyst added is actually transformed into the active species. Furthermore, if initiation is faster, the reaction can be performed at low temperature, allowing for improved selectivity in the metathesis reaction

Grubbs et al. have suggested that catalyst decomposition rates are related to the rates of initiation. NHC-complexes are exceedingly more chemically stable as compared to the bis-phosphine systems. Thermal decomposition appears to occur via the bimolecular coupling of the 14 electron complexes resulting from phosphine dissociation. As initiation and decomposition appear to proceed via a common intermediate, the depressed rates of initiation observed in catalyst **132** may account for its increased thermal stability over catalyst **131**.

Types of Olefin Metathesis Reactions

The four main classes of reactions catalyzed by olefin metathesis catalysts are ring-opening metathesis polymerization (ROMP), the acyclic version of which is known as acyclic diene metathesis polymerization (ADMET), ring-opening metathesis/cross metathesis (ROM/CM), ring-closing metathesis (RCM) and cross metathesis (CM) (Figure 1-10).

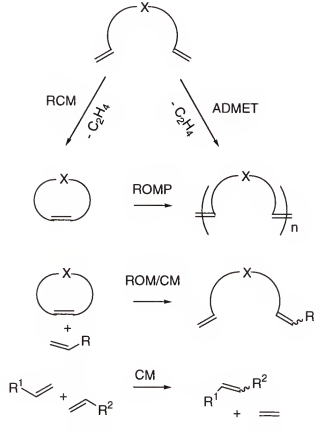


Figure 1-10. The different classes of olefin metathesis reactions

Ring-opening metathesis polymerization (ROMP)

Ring-opening metathesis polymerization (ROMP) was one of the first metathesis reactions to see major applicability. In this reaction a cyclic monomer undergoes metathesis, the reaction being driven by release of ring strain. The newly formed acyclic

alkylidene then attacks a second monomer, propagating the polymerization. The number of successes of ROMP in the synthesis of advanced materials abounds in the literature.[52] The method has been used in the synthesis of nanoclusters, luminescent materials, telechelic and ditelechelic polymers, liquid crystalline materials, conjugated polymers, electroactive polymers and a wide range of highly functionalized polymers.

A recent application of ROMP involved the synthesis of carbohydrate-functionalized polymers. One approach attached vancomycin to a norbornene-2,3-dicarbimide using $(PCy_3)_2Cl_2Ru{=}CHPh$, generating a vancomycin-derivatized ROMP polymer that showed increased potency against vancomycin-resistant enterococci (VREs) (Figure 1-11).

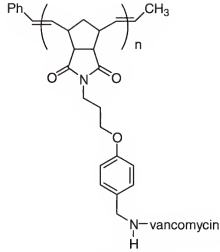


Figure 1-11. Vancomycin-derivatized ROMP polymer

Acyclic diene metathesis polymerization (ADMET), the acyclic version of ROMP, is generally performed using α,ω-dienes. The driving force of the reaction is believed to be the loss of ethylene that is permanently removed from the reaction mixture.

Many incidences of successful ADMET copolymerization of highly functionalized dienes containing ester, alcohol, ether, carbonate, and urethane functional groups have been reported. One interesting example is the preparation of main-chain ferroelectric liquid-crystal oligomers from a biphenyl-derived monomer using $(PCy_3)_2Cl_2Ru{=}CHCH_2Ph_2$ (Figure 1-12).

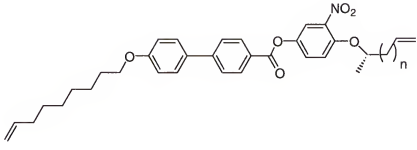
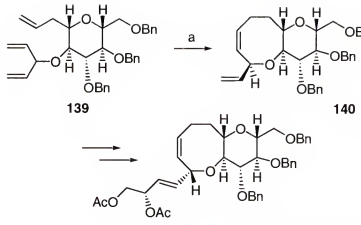


Figure 1-12. ADMET-active monomer for the synthesis of main-chain ferroelectric liquid crystal oligomers; n = 2 – 4

Ring-closing metathesis (RCM)

The second major type of metathesis reaction is ring-closing metathesis (RCM). As with ROMP, this reaction has seen widespread use, though its use has extended to natural product and peptide synthesis. RCM has served as the key step to close medium rings in molecules such as ciguatoxin (Scheme 1-33)[53], brevetoxin[54], and castanospermine as well as six to eight-membered cyclic peptides (Schemes 1-34 and 1-35).[55-59].

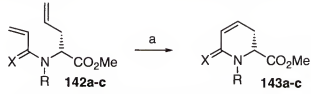


139 **140**

141 AB fragment of Ciguatoxin

a) $(PCy_3)_2Cl_2Ru$=CHPh (5mol%), CH_2Cl_2 (0.01M), rt, 95%

Scheme 1-33. RCM route to the AB-ring fragment of ciguatoxin



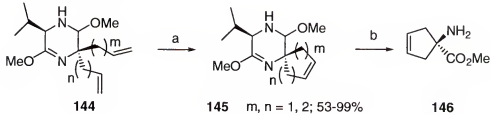
142a-c **143a-c**

a) $(PCy_3)_2Cl_2Ru$=CHPh (5 mol%), CH_2Cl_2, reflux

X = O; R = H,	20%	X = H_2;R = PMB	54%
R = PMB	93%	R = CH_2Fer	18%
R = CH_2Fer	89%	R = Boc	93%
		R = H	0%

(PMB = *p*-MeO-$C_6H_4CH_2$, Fer = Ferrocenyl-)

Scheme 1-34. Preparation of highly functionalized 6- and 7-membered amino esters or acrylic amides by RCM

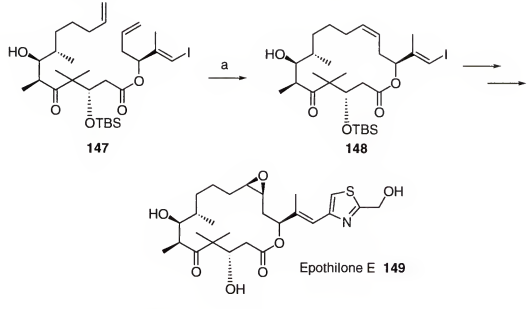


144 **145** m, n = 1, 2; 53-99% **146**
m + n = 5; <5%

a) $(PCy_3)_2Cl_2Ru$=CHPh (2 mol%); benzene, 20-100^{0}C, 5-23h; b) H^+

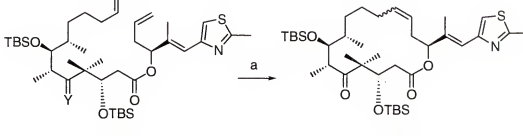
Scheme 1-35. Synthesis of cyclic amino esters by RCM

Macrocyclizations promoted by metathesis catalysts have also proven to be exceedingly useful, appearing in elegant syntheses of gloeosporone,[60] the epothilones[61-63] (Schemes 1-36 and 1-37) and lasiodiplodin[64] to name a few.



a) $(PCy_3)_2Cl_2Ru$=CHPh, CH_2Cl_2, (65%, *E/Z* = 2/1)

Scheme 1-36. Nicolaou's RCM / Stille approach to the epothilones

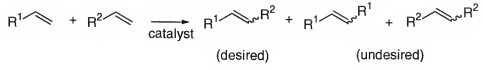


a) $(PCy_3)_2Cl_2Ru$=CHPh (50 mol%), CH_2Cl_2 (0.001M), rt, 24h (86%, *E/Z* = 1.7/1)

Scheme 1-37. Danishefsky's RCM approach to the epothilones

Cross metathesis (CM)

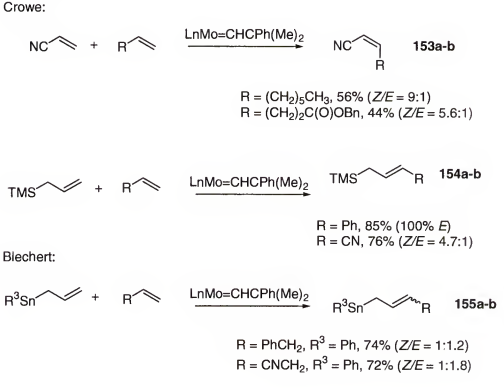
In the early years, the third type of metathesis reaction, cross metathesis (CM), had been largely disregarded as a synthetic method due to the problems associated with stereo- and regiocontrol. Of the three new alkenes potentially formed in the reaction, two result from undesired self-metathesis processes (Scheme 1-38).



Scheme 1-38. The potential products of the cross metathesis reaction

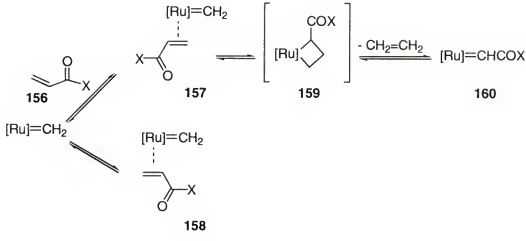
For the reaction to be synthetically useful, it would be necessary to determine a general method to minimize homocoupling and maximize the cross-coupling reaction. Before the development of Grubbs' second generation N-heterocyclic carbene catalyst **132**,[65] only a few successful examples had been reported. In 1995 and 1996 Crowe et al. demonstrated that cross metatheses, promoted by Schrock's molybdenum-based catalyst **128** and involving acrylonitrile or allylsilane as the coupling partner, gave moderate to good yields of the cross-metathesized product with little to no undesired self-metathesis products.[66,67] The low tendency of acrylonitrile and allyltrimethylsilane to dimerize accounted for the low yields of self-metathesis products observed (Scheme 1-39). In the case of acrylonitrile, although alkyl-substituted olefins bearing electron-withdrawing groups gave low yields, high *cis*-selectivity was observed in all cases. In the cross metathesis of allylsilanes with a variety of *para*-substituted styrenes, Crowe showed that bulkier alkyl groups on the silyl alkenes led to increased *trans* selectivity without adversely affecting the yields. In 1997, Blechert and coworkers used the cross metathesis reaction in the preparation of synthetically important allyl stannanes.[68] Despite the low

stereoselectivity observed, yields of the desired cross-metathesized products were relatively high, ranging from 67-78% with a range of alkenes (Scheme 39).



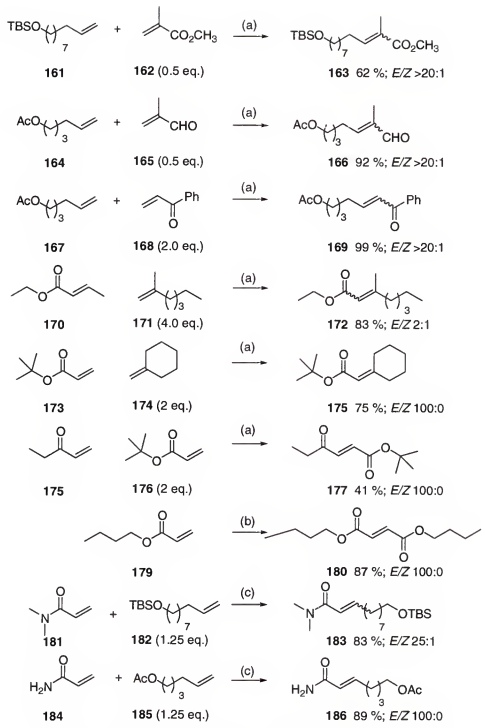
Scheme 1-39. Intermolecular cross metathesis

With the development of the second generation Grubbs' catalyst **132**, cross metathesis chemistry met with much greater success as the range of olefins that could efficiently participate in the reaction due to the catalyst's enhanced reactivity and functional group tolerance broadened significantly. Grubbs and coworkers established that α,β-unsaturated carbonyls react directly with catalyst **132** generating, *in situ*, the highly reactive enoic carbene **160** (Scheme 1-40).[69]



Scheme 1-40. *In situ* generation of enoic carbene

Under carefully controlled conditions, Grubbs et al. reported high yielding cross-metathesis reactions involving trisubstituted olefins as well as highly functionalized α-carbonyl olefins such as esters, ketones, aldehydes and amides.[70,71] Furthermore, catalyst **132** was found to promote not only the dimerization of α,β-unsaturated carbonyl compounds in high yields, but also the cross metathesis of two different α-carbonyl olefins, albeit in moderate yields.[69] Steric bulk in close proximity to the reacting olefin appeared to increase the *cis/trans* selectivity, with disubstituted olefins and ketones showing increased stereoselectivity over monosubstituted derivatives and aldehydes respectively (Scheme 1-41).



161 **162** (0.5 eq.) **163** 62 %; *E*/*Z* >20:1

164 **165** (0.5 eq.) **166** 92 %; *E*/*Z* >20:1

167 **168** (2.0 eq.) **169** 99 %; *E*/*Z* >20:1

170 **171** (4.0 eq.) **172** 83 %; *E*/*Z* 2:1

173 **174** (2 eq.) **175** 75 %; *E*/*Z* 100:0

175 **176** (2 eq.) **177** 41 %; *E*/*Z* 100:0

179 **180** 87 %; *E*/*Z* 100:0

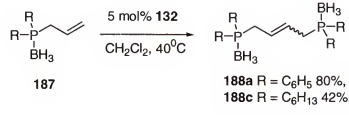
181 **182** (1.25 eq.) **183** 83 %; *E*/*Z* 25:1

184 **185** (1.25 eq.) **186** 89 %; *E*/*Z* 100:0

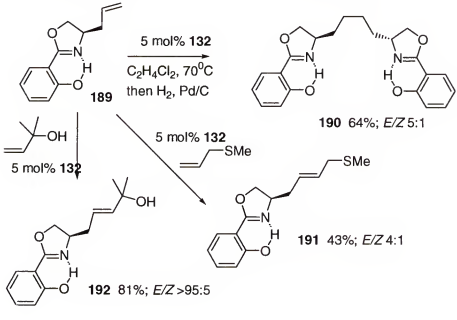
(a) 5 mol% catalyst **132** at 0.1-0.3M in refluxing CH_2Cl_2 for 3 h; (b) 5 mol% catalyst **132** at 0.4M in refluxing CH_2Cl_2 for 3 h; (c) 5 mol% catalyst **132** at 0.2M in refluxing CH_2Cl_2 for 15 h

Scheme 1-41. Cross metathesis of α,β-unsaturated carbonyl compounds

More recently, reports of successful cross metatheses with allyl sulfides, N-allyl amines, and borane complexes of allyl phospines have appeared (Scheme 1-42).[72] Their usefulness in the synthesis of bidentate and tridentate chiral ligands has been demonstrated. In most cases, moderate to excellent control of cis/trans geometry has been achieved.



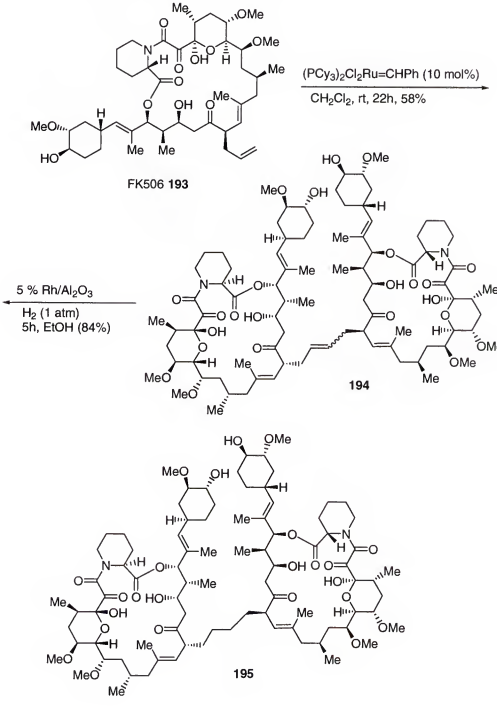
Application to the synthesis of 2-oxazoylphenol chiral ligands



Scheme 1-42. Cross metatheses of functionally diverse olefins

In recent years, the cross metathesis reaction has been successfully applied to various syntheses including the design of unnatural amino acids and analogues of natural products, namely jasmonic acid. The dimerization of the immunosuppresant FK506 to yield FK1012 was achieved in 58% yield using Grubbs' first generation catalyst,

$(PCy_3)_2Cl_2Ru$=CHPh (Scheme 1-43).[73] Although poor stereoselectivity was observed, the isomers were separable by chromatography. Furthermore, the hydrogenated product was found to be highly active in functional, cellular assays.

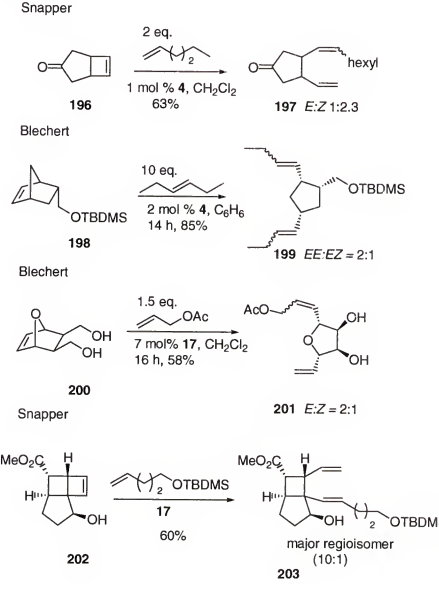


Scheme 1-43. Synthesis of FK1012 and $FK1012H_2$ by olefin cross metathesis of FK506

Ring-opening metathesis/cross metathesis (ROM/CM)

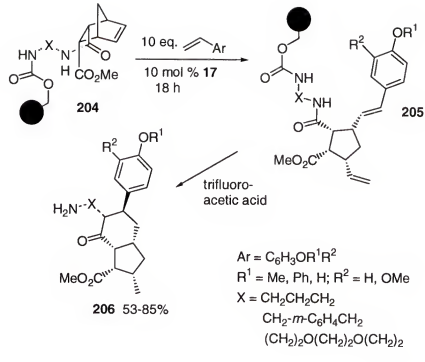
Similar to the acyclic cross metathesis reaction is the ring-opening metathesis/cross metathesis version, unique from its acyclic counterpart in that one of the alkenes is replaced by a strained cyclic olefin, such that release of ring strain drives the reaction. As this introduces the possibility of ROMP, the reaction is generally performed at relatively dilute concentrations (*ca.* 0.1M) and in the presence of a significant excess of the acyclic alkene. Again, only with efficient control of regio- and stereoselectivity is the reaction synthetically useful. In 1995, Snapper and coworkers reported the first success in this new variation of metathesis chemistry with the preparation of functionalized monomeric products. They reacted a series of simple terminal alkenes with a variety of symmetrical cyclobutenes in the presence of Grubbs' ruthenium vinylalkylidene catalyst **130** (Scheme 1-44).[74] Success with the use of internal acyclic alkenes did not come until a year later, when Blechert reported the ring-opening cross metathesis of a series of functionalized norbornene derivatives with *trans*-hex-3-ene using the same ruthenium based catalyst as Snapper.[75] Blechert, in 1997, demonstrated that the molybdenum alkylidene **128** and the ruthenium benzylidene **131** were also active catalysts for ring-opening cross-metathesis reactions.[76] As anticipated, problems arose with sterically hindered acyclic substrates, and less electron rich alkenes such as acrylonitrile only underwent cross metathesis with the more active molybdenum alkylidene **128**. At about the same time, Snapper published the application of this metathesis chemistry to the synthesis of bicyclo[6.3.0] ring systems with excellent regioselectivity.[77] Later the same year, Cuny and coworkers introduced the use of polymer bound norbornene substrates to minimize ROMP and reported complete regioselectivity in the ring-opening cross

metathesis between electron rich styryl ethers and resin-bound norbornenes attached to Wang resin via primary diamine linkers (Scheme 1-45).[78]



Scheme 1-44. Early successes using the ROM/CM reaction

Though seemingly variable and unpredictable in terms of regio- and stereoselectivity, in some cases, the ring-opening cross-metathesis reaction is highly efficient and provides a new method for the synthesis of functionally diverse alkenes, not easily accessible via other known routes.



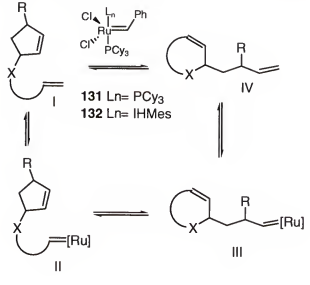
Scheme 1-45. ROM/CM on a polymer support

The early successes have been extensively reviewed by Grubbs, Gibson, Armstrong and Wright, with the most recent compilation by Fürstner in 2000.[79-83] Since then, the ring-opening metathesis/cross metathesis success rate has increased dramatically with major advances in the application of domino metathesis processes, whereby the closing of one ring promotes the opening of another that can potentially undergo a third metathesis process. This may entail either intramolecular ring closure with a tethered olefin or intermolecular cross metathesis.

Domino Ring-Closing Metathesis/Ring-Opening Metathesis (RCM/ROM)

The driving force of this process is thought to be the enthalpic gain derived from the loss of ring strain of the reactant cyclic olefin. In cases where the cyclic olefin is not highly strained, the loss of a small molecule, generally ethylene, is thought to drive the

reaction. In this process, the initial metathesis process is thought to occur on the terminal olefin that is tethered to the cyclic olefin **I** (Scheme 1-46). The reactive alkylidene **II** thus formed has two options. A reaction between **I** and **II** would lead to the formation of dimers. Domination of the intramolecular metathesis process with the endocyclic double bond would, however, result in ring closure. This ring closure promotes opening of the cyclic alkene, resulting in formation of a new ring system via carbene complex **III**. Isolation of high yields of **IV** depends on reduction of cross metathesis of **III** with **I**.

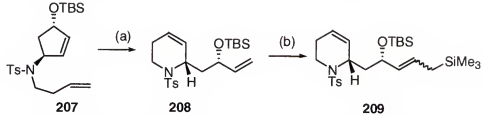


Scheme 1-46. Ruthenium-catalyzed domino ring-closing /ring-opening metathesis

Blechert et al. have extensively explored tandem ring-closing metathesis/ring-opening metathesis (RCM/ROM) rearrangements of unstrained olefinic carbocycles with alkenyl side chains. In recent years, a myriad of syntheses dependent upon this metathesis cascade have been reported from the laboratories of Blechert.

In 1999, they demonstrated their success with domino RCM/ROM through their synthesis of (-)-halosaline, a piperidine alkaloid isolated from *Haloxylon Salicornicum*.[84] Initial attempts resulted in low yields of the desired intermediate **209**. A one pot

procedure, requiring initial RCM/ROM followed by cross metathesis with allyltrimethylsilane to elongate the chain and approach the core of halosaline, failed to accomplish the final cross metathesis reaction. Use of Schrock's more reactive molybdenum-based catalyst **128** promoted an initial cross metathesis between allyltrimethylsilane and **207**, precluding the required ring rearrangement. Although Blechert et al. were successful in generating the desired intermediate by isolating the product of the ring rearrangement and subjecting it to intermolecular cross metathesis with the terminal olefin, the yield was moderate (58%) (Scheme 1-47).

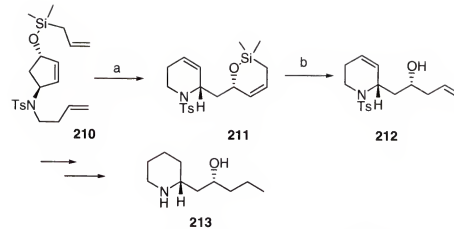


207 **208** **209**

a) 5 mol % **131**, CH_2Cl_2, rt., 5h (96%); b) 3 eq. allyltrimethylsilane, 10 mol % **128**, CH_2Cl_2, (58%)

Scheme 1-47. Manipulation of varying reactivity of Ru- and Mo-based catalysts to achieve RCM/ROM and subsequent CM in two steps

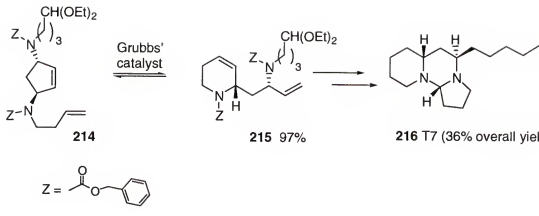
An increased yield of 78% was achieved by replacing the final cross metathesis step with a second ring-closing metathesis process. By tethering the required allylsilane to the endocyclic olefin in the form of a protecting group, the domino process occurred smoothly in one pot (Scheme 1-48). Subsequent exposure to tetrabutylammonium fluoride (TBAF) gave halosaline precursor **212** in 78% yield.



a) 5 mol% $(PCy_3)_2Cl_2Ru$=CHPh, CH_2Cl_2, rt., 4h. b) 3 eq.TBAF, -78^{0}C-warm up,CH_2Cl_2

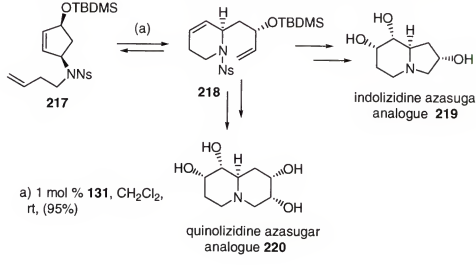
Scheme 1-48. Blechert's synthesis of (-)-halosaline (**213**)

Blechert extended this methodology to the synthesis of the tetraponerines, alkaloids isolated from the venom of the New Guinean ant *Tetraponera sp.*[85] He demonstrated that the equilibrium of the metathesis rearrangement could be tuned based on the choice of the N-protecting groups. In the case of the *trans* cyclopentene derivatives, the benzyloxycarbonyl group allowed quantitative conversion from starting material to product. The *o*-ntirobenzosulphonyl group was a better protecting group for the *cis* derivatives. As in the halosaline synthesis, Blechert utlilized the metathesis reaction to transfer stereochemical information from readily available carbocyclic starting materials to heterocyclic products. He achieved the synthesis of four of the eight tetraponerines, T4, T6, T7, and T8. (Scheme 1-49, representative)



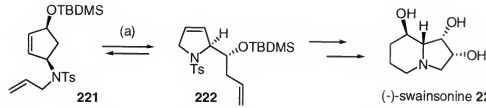
Scheme 1-49. Blechert's synthesis of tetraponerine, T7, using RCM/ROM

Blechert successfully applied the RCM/ROM methodology to the synthesis of indolizidine (**219**) and quinolizidine (**220**) azasugar analogues (Scheme 1-50).[86]



Scheme 1-50. Azasugar analogues synthesized using RCM/ROM as a key step

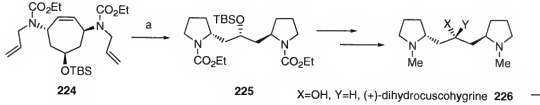
Further application of the azasugar studies led to the synthesis of the indolizidine alkaloid (-)-swainsonine (**223**) (Scheme 1-51).[87]



a) 5 mol % **131**, ethylene, CH_2Cl_2, 40^0C, 1 h, (98%)

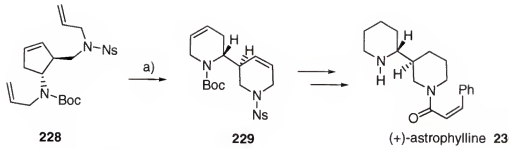
Scheme 1-51. RCM/ROM approach to (-)-swainsonine (**223**)

Drawing on the early success with halosaline, Blechert applied a cascade RCM/ROM/RCM sequence to the syntheses of (+)-dihydrocuscohygrine (**226**),[88] cuscohygrine (**227**)[88] and (+)-astrophylline (**230**).[89] In each case, starting from a bisalkenyl-substituted cycloalkene, Grubbs' second generation catalyst, (IHMes)(Cy_3P)Cl_2Ru=CHPh **132**, promoted a tandem ring rearrangement metathesis to yield a bis-dihydropyrrole system in the cases of dihydrocuscohygrine and cuscohygrine (Scheme 1-52) and a bis-piperdine in the case of astrophylline (Scheme 1-53).



a) (i) (IHMes)(Cy_3P)Cl_2Ru=CHPh, 5 mol%, CH_2Cl_2, reflux, 36h; (ii) H_2, Pd/C, EtOH, 72%

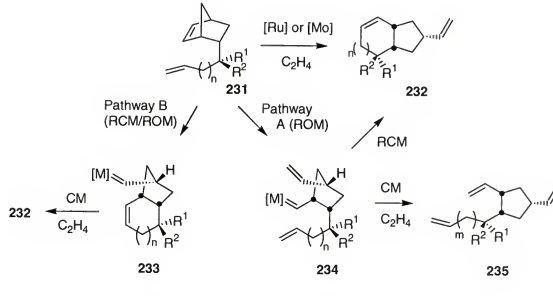
Scheme 1-52. RCM/ROM/RCM tandem ring rearrangement metathesis in the syntheses of (+)-dihydrocuscohygrine and cuscohygrine



a) (IHMes)(Cy_3P)Cl_2Ru=CHPh, 1 mol%, CH_2Cl_2, 40^0C, 2h, (82%)

Scheme 1-53. RCM/ROM/RCM tandem rearrangement metathesis in the synthesis of (+)-astrophylline.

In 1998, Blechert et al. reported a method for the synthesis of [n.3.0] bicycloalkenes by a combined RCM/ROM/CM cascade of alkenyl substituted norbornene derivatives (Scheme 1-54).[90]



Scheme 1-54. Mechanistic considerations of the RCM/ROM/CM process

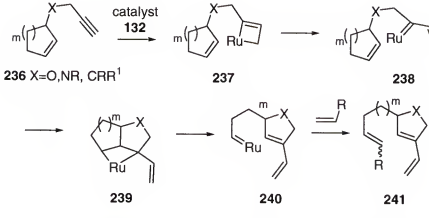
It appeared that two separate mechanisms, A and B, were responsible for formation of the linear-fused bicyclic products **232**. Blechert and coworkers proposed that in systems that led to the formation of five-, six-, and seven-membered rings, the initial metathesis process occurred at the terminal olefin. Ring closure, in effect, resulted in

opening of the norbornene bicycle and formation of the reactive alkylidene intermediate **233**.

On the other hand, reactions leading to formation of eight-membered rings participated in a two step reaction whereby formation of the monocyclic alkylidene **234** was followed either by a ring-closing metathesis to generate the bicyclic product **232** or by a cross metathesis with ethylene to yield **235**. Blechert et al. offered no explanation for the mechanistic differences. Also investigated were the differences in catalyst reactivity. Schrock's molybdenum catalyst **128** was found to readily promote metathesis of sterically hindered olefins and enabled the formation of eight-membered rings, whereas in both cases, use of Grubbs' ruthenium catalyst resulted in low yields. A stereochemical effect was also observed. When a bulky silyloxy group was placed at R^1, the reaction gave yields 15-20% higher than the same group at R^2. Again no explanation for these effects was offered.

In 2001, Blechert added another aspect to the repertoire of cascade reactions. By tethering an alkynyl side chain to the cyclic olefin, the metathesis reaction was rendered irreversible (Scheme 1-55).[91] The initial metathesis process occurred selectively at the triple bond yielding vinyl carbene complex **238**. A [2+2] cycloaddition to the endocyclic olefin and subsequent cycloreversion afforded the rearranged carbene. A final cross metathesis (CM) with ethylene generated the bis-alkynyl substituted heterocycle **241**. Though Blechert and coworkers reported success with the RCM/ROM/CM cascade to generate dihydrofurans and dihydropyrroles, they acknowledged that the extent of product formation was highly dependent on the ring size of the cyclic olefin as well as the length of the alkynyl chain. The best systems for the synthesis of dihydropyrroles were

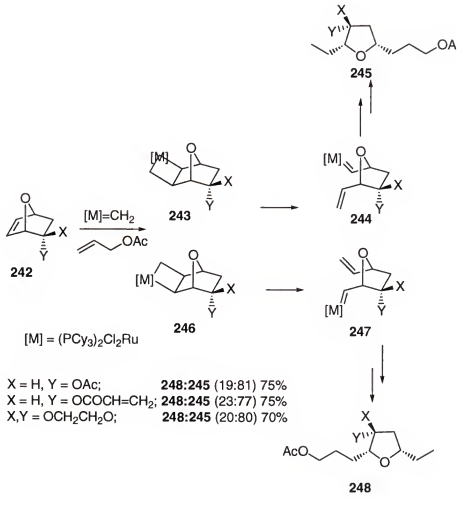
found to be five and six-membered carbocycles with propargyl side chains, giving yields upwards of 60%. Variation in the length of the side chain and the position of the triple bond to attempt larger N-heterocyclic rings resulted in low yields of metathesized product. Dihydrofurans were only successfully synthesized from propargyl substituted cyclopentenes.



Scheme 1-55. RCM/ROM/CM cascade with alkynyl-tethered cycloalkenes

In 1999, Arjona and coworkers studied the ROM/CM of variably substituted 7-oxanorbornene systems (Scheme 1-56).[92] Their major goal was to study the regiochemical aspects of the reaction. They demonstrated that in the presence of a ketone or alcohol at C2 on the bicycle no regioselectivity was detected. When the Y substituent was an acetate or acrylate, however, the general trend in regioselectivity for the 2-substituted 7-oxanorbornene derivatives seemed to favor formation of the metal alkylidene intermediate on the less hindered side of the bicyclic system (**244**). The cross metathesis therefore placed the added side chain on the less hindered side (**245**). Arjona et al. proposed that the regioselectivity was determined by a combination of steric, electronic and complexation effects. Based on their studies, the cycloaddition of the carbene to the bicyclic alkene could have been influenced by the relative steric bulk of

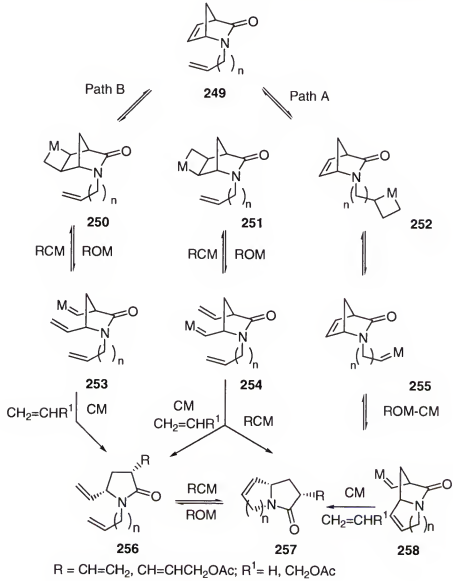
substituents in positions X and Y on the ring system. Alternatively, the bias could have arisen in the cross metathesis step where steric hindrance or complexation effects in the carbenes directed the regioselectivity of the products.



Scheme 1-56. Regiochemistry of ROM/CM of 2-substituted 7-oxanorbornenes

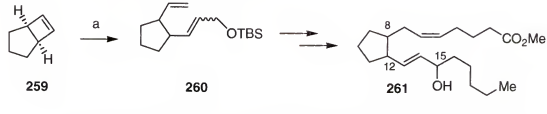
In 2002, Arjona et al. extended the study to the synthesis of pyrrolidizidines by RCM/ROM/CM of variably substituted 2-azanorbornenes (Scheme 1-57).[93] Once again they proposed the functioning of two mechanistic pathways, A and B, to account for the observed product distribution. In the case where the initial metathesis process occurred at the terminal olefin (A), the major product **257** was achieved by a tandem RCM/ROM/

CM. Modest yields of 55-65% suggested the possibility of stability and therefore diminished reactivity of the intermediate complex **255** caused by coordination of the metal to the carbonyl group. When the initial cycloaddition occured on the bicyclic olefin (pathway B), two regioisomeric carbenes, **253** and **254**, were possible. These offered some explanation for the isolation of the bis-alkynyl substituted lactam **256**, which could be converted to the bicyclic lactam **257** by a second RCM process.



Scheme 1-57. Regioselectivity of the RCM/ROM/CM of 2-azanorbornenones

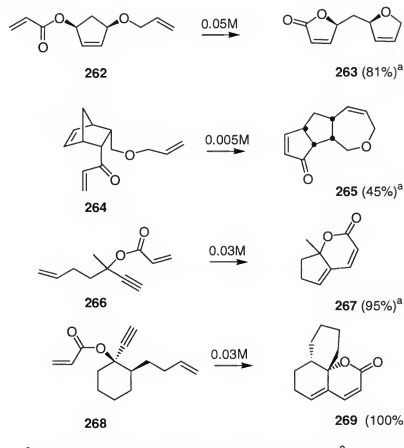
Snapper's laboratory has utilized ROM/CM of a bicyclobutane derivative as a key step in the synthesis of isoprostane analogues (Scheme 1-58).[94] Upon exposure of cyclobutene **259** to the first generation Grubbs' catalyst **131** in the presence of TBS-protected allyl alcohol, the ROM/CM product **260** was isolated in 56% yield as a mixture of stereoisomers (*Z:E* 2.3:1). The mixture was carried forward and four stereochemically distinct isoprostane analogues were achieved.



Scheme 1-58. Snapper's synthesis of analogues of isoprostane via ROM/CM

Grubbs and coworkers reported success with tandem RCM/ROM/RCM as well as tandem RCM to synthesize α,β-unsaturated lactones and enones.[95] Using the more active second generation catalyst **132** containing the N-heterocyclic carbene, they demonstrated the ability of the catalyst to promote selective tandem metathesis of notoriously difficult α,β-unsaturated carbonyl substrates (Scheme 1-59). With bis-alkenyl cyclopentenes containing electronically diverse terminal olefins **262**, selective metathesis at the more electronically rich, reactive alkene promoted ring opening at the carbocyclic olefin. A final cross metathesis between the newly generated carbene and the α,β-unsaturated carbonyl moiety generated the rearranged α,β-unsaturated lactone **263**. In the case of disubstituted norbornenes **264**, angular fused tricyclic systems resulted. Grubbs reported tremendous success in the synthesis of linear-fused bicycles taking advantage of the high

selectivity involved in the enyne metathesis. 6-5-6- and 6-6-6- fused tricyclic compounds were achieved.

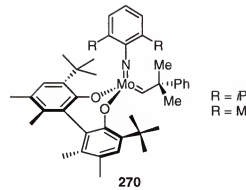


[a] conditions: 5 mol% $(IHMes)(Cy_3P)Cl_2Ru{=}CHPh$, 40^0C, CH_2Cl_2, 6-12 h

Scheme 1-59. Tandem RCM/ROM to α,β-unsaturated lactones and enones

Catalytic Asymmetric Olefin Metathesis

With the development of chiral metathesis catalysts, scientists have begun to address the ultimate goal of olefin metathesis, that is, to convert simple, achiral or racemic substrates into complex non-racemic organic molecules. The first chiral catalysts were based on Schrock's molybdenum alkylidene **128**.[96,97] In a collaborative effort with Hoveyda et al., Schrock and coworkers studied the performance of a range of chiral molybdenum based catalysts (Figure 1-13).[98]



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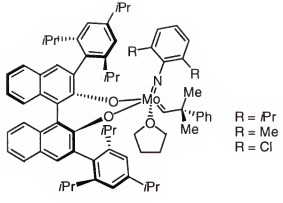

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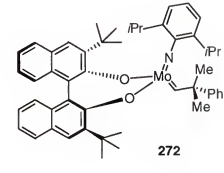

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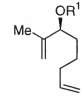
Figure 1-13. Some highly active, molybdenum-based asymmetric olefin metathesis catalysts

They demonstrated the high substrate specificity of the catalysts and established that, with subtle changes in the alkoxide and imido ligands, the catalysts could be tuned to effect the desired metathesis reaction in good to excellent yields with *ee*'s as high as 99%. Aside from ROMP, RCM was the first reaction to which chiral catalysts were applied. Schrock and Hoveyda observed that catalyst **270** achieved resolution of silyl ethers **273a** and **2743b** and ethers **274a** and **274b** with excellent levels of enantiocontrol (K_{rel}>20) (Scheme 1-60).[99,100] Via a RCM of one enantiomer of a racemic mixture of 1,6-dienes, the optically enriched 1,6 diene and the cyclic RCM product could be isolated. The same catalyst, however, gave poor yields and low *ee*'s with structurally similar 1,7-dienes.

(*R*)-**273a**; R^1 = Me; k_{rel} > 25; catalyst **270**
(*R*)-**273b**; R^1 = H; k_{rel} = 23; catalyst **270**

(*S*)-274a; R^1 = *n*-pentyl; k_{rel} = 10; catalyst **270**
(*S*)-**274b**; R^1 = *sec*-butyl; k_{rel} = 23; catalyst **270**
(*S*)-**274c**; R^1 = cyclohexyl; k_{rel} = 1; catalyst **270**



(*S*)-**275a**; R^1 = TES; k_{rel} = 24; catalyst **271**
(*S*)-**275b**; R^1 = TBS; k_{rel} = 25; catalyst **271**

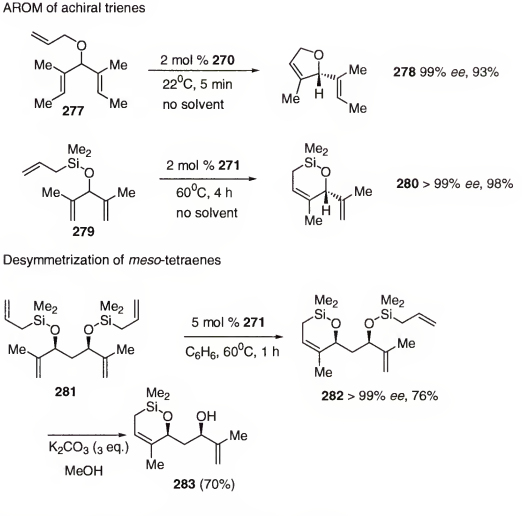
(*S*)-**276a**; R^1 = Me; R^2 = *n*-pentyl; k_{rel} > 25; catalyst **271**
(*S*)-**276b**; R^1 = Me; R^2 = cyclohexyl; k_{rel} > 25; catalyst **271**
(*S*)-**276c**; R^1 = H; R^2 = MeCH=CHMe; k_{rel} = 21; catalyst **270**
(*S*)-**276d**; R^1 = H; R^2 = cyclohexyl; k_{rel} > 25; catalyst **270**

Scheme 1-60. Mo-catalyzed kinetic resolution of 1,6 and 1,7-dienes

High levels of enantioselectivity were restored by substituting the BIPHEN-derived ligand with a BINOL-derived species to generate catalyst **271**.[101] Schrock and Hoveyda concluded that biphenolate **270** best catalyzes formation of five-membered ring systems, whereas the binaphtholate **271** gives better enantiocontrol in the synthesis of six-membered analogues. In the study of variably substituted 1,7-dienes, however, it was acknowledged that subtle differences in the substrate could reverse the general trend, making it difficult to predict which catalyst would function with the highest

enantiocontrol. This study highlighted the need for a diverse set of chiral catalysts that could be screened for the best results.

Based on the success with dienes, achiral trienes were examined as substrates for the ARCM (Scheme 1-61). Desymmetrization of **277** and **279** was achieved by exposure to 2 mol% of the biphen catlayst **270**.[102] The reaction was carried out at 22°C and was complete within five minutes. The binol catalyst successfully desymmetrized *meso* tetraene **281**, producing optically pure siloxane **282** in 76% yield with *ee* >99% (Scheme 1-61).



Scheme 1-61. Mo-catalyzed ARCM of trienes and tetraenes

Burke's synthesis of *exo*-brevicomin (**286**) represents the first application of asymmetric olefin metathesis in target-directed synthesis.[103] A crucial step was the ARCM with catalyst **270** to give the key intermediate **285** in 90% yield and 59% *ee* (Scheme 1-62). Schrock and Hoxeyda later reported that the ARCM of acetals was best achieved with a hybrid biphen-, binol system.

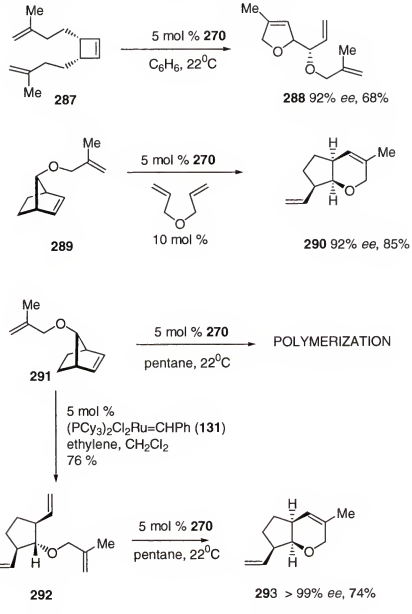
284 **285** 59% *ee*, 90% *exo*-brevicomin **286**

Scheme 1-62. Enantioselective synthesis of exo-brevicomin

Although most of the asymmetric work done thus far has focused on the RCM reaction, asymmetric molybdenum systems have successfully catalyzed a variety of tandem reactions. Several substrates underwent a tandem AROM/RCM using biphen-catalyst **270** (Scheme 1-63).[104] Excellent enantioselectivity (92-99%) was observed. In the case of *meso*-bicycle **289**, diallyl ether was required for the reaction to proceed.[105] Based on earlier mechanistic studies, Schrock et al. proposed that the molybdenum neophylidene was too bulky to react with the hindered norbornyl alkene and therefore first reactd with allyl ether, generating the less bulky methylidene catalyst, which could then react with the endocyclic alkene. This depressed reaction rate was not observed with the diastereomer of **289**, which had the *O*-allyl chain opposite the internal olefin (**291**).

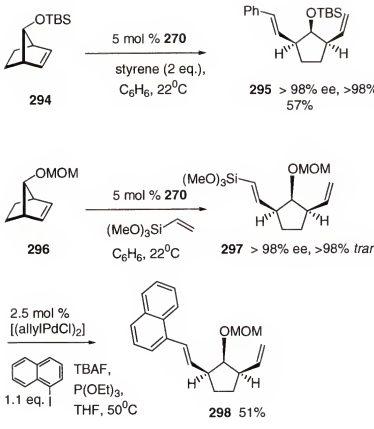
On the contrary, norbornene **291** reacted so swiftly with catalyst **270** that ROMP was the dominant reaction. Schrock and Hoveyda were able to overcome the increased reactivity by first opening the bicycle with ethylene in the presence of achiral catalyst

$(PCy_3)_2Cl_2Ru$=CHPh (**131**). The newly formed triene **292** was then exposed to catalyst **270** to generate the linear fused bicycle **293** in 74% yield with >99% *ee*.



Scheme 1-63. Tandem AROM/RCM of substituted norbornenes

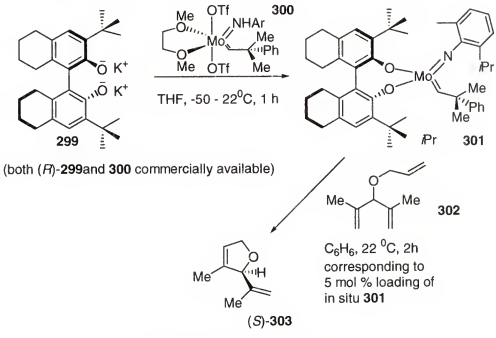
Tandem AROM/CM reactions have also been studied. With styrene and trimethoxyvinylsilane as the coupling partners, modest yields were observed in the norbornene systems, yet enantioselectivity was high (Scheme 1-64).[106]



Scheme 1-64. Mo-catalyzed AROM/CM to yield optically enriched, highly functionalized cyclopentanes

In an attempt to render their catalyst systems more general and "user friendly", in 2001 Schrock and Hoveyda developed a new chiral molybdenum-based catalyst **272** bearing a "biphenol-type" ligand synthesized from readily available optically pure binaphthol.[107] Not only was this beneficial in terms of lowered cost of preparation, but the hope was that this catalyst would exhibit properties of both the BIPHEN- and BINOL complexes, thereby expanding its scope. A major advantage of this catalyst over the others is that, not only can it be prepared from commercially available starting materials, but also that it need not be isolated and purified before use. Schrock and Hoveyda published an *in situ* preparation of the catalyst and reported that the active catalyst did not

possess the extreme sensitivity to moisture displayed by its analogues and could be handled in a regular fume hood (Scheme 1-65).

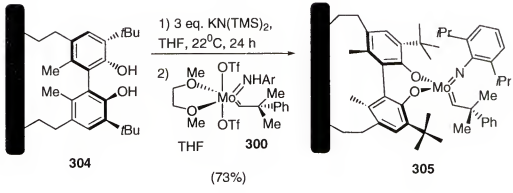


Scheme 1-65. *In situ* preparation and use of chiral catalyst **272**

They confirmed that the new catalyst performed just as well or better in the RCM of the substrates tested previously and exhibited generality, catalyzing the formation of both five- and six-membered rings. It functioned equally well in the tandem AROM/CM of the norbornene systems previously explored.

Further addressing the issue of practicality, Schrock and Hoveyda reported the synthesis of a recyclable catalyst bearing a chiral ligand attached to a polymer backbone via a nonlabile tether (Scheme 1-66).[108] It was shown to efficiently catalyze the ARCM and the tandem AROM/RCM and AROM/CM reactions of many of the previously studied substrates. Although the catalyst was not as highly reactive as the BIPHEN and BINOL complexes, giving low yields particularly with sterically demanding substrates, in

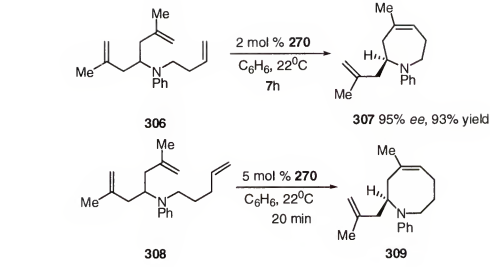
most cases, comparable levels of asymmetric induction were observed. The desymmetrization and kinetic resolution processes were especially successful. Though preparation of the catalyst is somewhat involved, the advantages cannot be overlooked. Not only is workup greatly simplified, with filtration achieving catalyst removal, but reactions can also be accelerated by increasing substrate concentration. Schrock and Hoveyda also showed that the catalyst could be efficiently recycled with enantioselectivity being retained through three cycles. Catalyst activity, on the other hand, remained high in the first two cycles, but diminished in the third cycle.



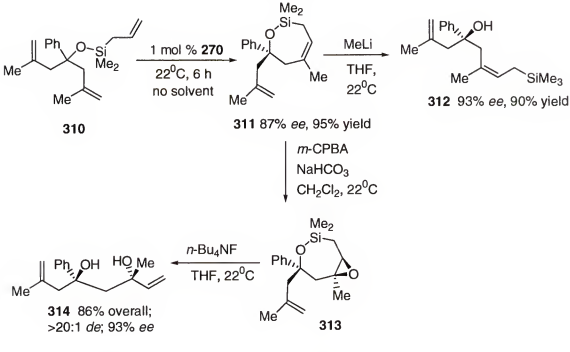
304 300 305

Scheme 1-66. Synthesis of supported chiral catalyst

In the last two years, Schrock and Hoveyda have confirmed the ability of their catalyst systems to generate optically enriched tertiary unsaturated cyclic ethers, alcohols and amines (Schemes 1-67 and 1-68).[109-112] Though the reactions are generally carried out at room temperature in benzene, the same processes may be performed in the absence of solvent with little or no loss in yield or enantioselectivity. Yields are moderate to high and, with the right choice of catalyst, excellent levels of enantiocontrol are observed. In the case of the amines, factors such as olefin substitution affect the reactivity and selectivity of the catalysts.

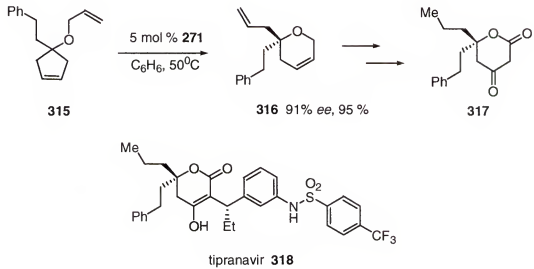


Scheme 1-67. Asymmetric synthesis of medium-ring amines by ARCM



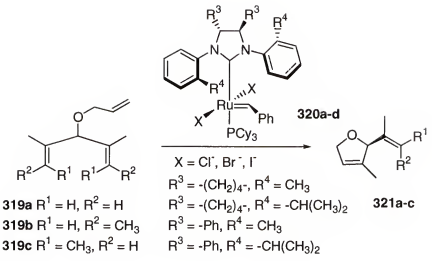
Scheme 1-68. Enantioselective synthesis of cyclic tertiary ethers by ARCM and subsequent conversion to tertiary alcohols

The tandem ARCM/ROM was used in the synthesis of the lactone moiety **317** of the anti-HIV agent tipranavir (**318**) (Scheme 1-69).[109] The tertiary cyclic ether **315** was converted to dihydropyran **316** in 95% yield and 91% *ee* in the presence of 5 mol% of **271**.



Scheme 1-69. Application of ARCM toward the synthesis of tipranavir

In 1999, Grubbs et al. disclosed the synthesis of their ruthenium-based chiral catalysts, prepared in three steps from commercially available starting materials including optically pure diamines and the first generation catalyst **131** (Scheme 1-70).[113] The catalysts were capable of catalyzing the asymmetric RCM of mono-, di- and trisubstituted olefins, but high *ee*'s were observed only with (*E*)-trisubstituted olefins (63-90%). The dihydrofuran derivatives resulting from the RCM of the (*E*)-trisubstituted olefins were obtained in excellent yields (82-90%). Grubbs and coworkers observed that enantioselectivity was dramatically increased upon changing the halide ligand from chloride to bromide to iodide *in situ* by addition of excess LiBr or NaI.



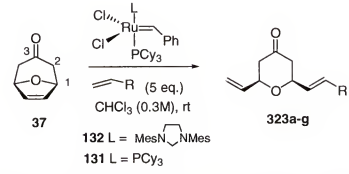
Scheme 1-70. Asymmetric RCM with ruthenium-based chiral catalysts

CHAPTER 2
RESULTS/DISCUSSION

Intermolecular Ring-Opening Metathesis/Cross Metathesis

The goal of the early studies was to investigate the behavior of oxabicyclo[3.2.1] octene derivatives in the presence of Grubbs' olefin metathesis catalysts. Initially, investigations centered around the parent compound, 8-oxabicyclo[3.2.1]oct-6-en-3-one[23] (**37**). The intermolecular ring-opening metathesis/cross metathesis between **37** and a series of electronically diverse terminal alkenes was explored (Scheme 2-1).[114] The reactions were carried out at room temperature at a concentration of 0.3M of the bicyclic ketone in chloroform. Five equivalents of the partner olefin and 1 mol% of catalyst **132** were added. Both NMR spectroscopy and thin layer chromatography were used to monitor the progress of the reactions. The ROM/CM appeared to be highly selective for the formation of *E*-alkenes, with any *Z*-isomer being removed by column chromatography. Not surprisingly, the efficiency of the metathesis reaction was directly related to the electronic nature of the donor alkenes. The electron rich alkenes, styrene and 1-hexene, afforded the highest yields of ring-opened cross-metathesized products Catalyst **132** proved superior to catalyst **131** in all instances except in the reaction with 1-hexene where lower yields resulted with the more reactive **132**. An additional compound resulting from a second cross metathesis between the initial ring-opened cross-metathesized product and another molecule of 1-hexene accounted for the low yields of desired product. As the alkenes became less electron rich or more sterically hindered, as in the case of 2-bromostyrene, the yields decreased. Not surprisingly, with the electron

poor alkenes acrylonitrile and methacrylate, the yields were low despite attempts to drive the reaction with increased temperature, increased catalyst loading and large excess of the donor olefin. Recent literature supports the limited reactivity of electron poor alkenes in cross metathesis.[66,67]



Scheme 2-1. ROM/CM of 8-oxabicyclo[3.2.1]oct-6-en-3-one with terminal alkenes

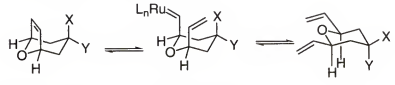
Table 2-1. ROM/CM of 8-oxabicyclo[3.2.1]oct-6-en-3-one with terminal alkenes

Pyran	Alkene	-R	Catalyst	Yields (%)
323a	Styrene	-Ph	**132**	83
323b	2-bromostyrene	-*o*-BrPh	**132**	65
323c	1-hexene	$-(CH_2)_3CH_3$	**131**	89
323d	allyl bromide	$-CH_2Br$	**132**	71
323e	4-bromo-1-butene	$-CHCH_2Br$	**132**	72
323f	Methylacrylate	$-CO_2Me$	**132**	33
323g	Acrylonitrile	-CN	**132**	10

The progress of the ROM/CM reaction could be monitored by NMR. This led to the discovery that the reaction was an equilibrium process, preventing total conversion of starting material to product. The representative reaction between styrene and the bicyclic ketone was monitored by NMR and once equilibrium was reached, approximately 90% completion by NMR, the addition of a known quantity of starting material resulted in rapid return to equilibrium ratios. This indicated that the reaction was reversible. The reversibility of the reaction was confirmed by the addition of Grubbs' catalyst **132** to the

isolated ring-opened cross-metathesized product. As expected, the ring-opened product underwent ring closure to produce styrene and the original bicyclic ketone.

Upon consideration of the system it was hypothesized that if the molecule was hindered in such a way that the conformation necessary for ring closure, where the two appendages adopt a diaxial relationship (**325**), became highly unfavorable, the reaction would become irreversible and the product yield could potentially be increased (Scheme 2-2). The introduction of a bulky group at the C3 position would provide such a destabilization as it would result in an additional set of diaxial interactions absent in the ketone. By simple reduction of the ketone to the corresponding *endo* alcohol and conversion to the bulky silyl ether, the reaction should then become irreversible and the yield of the desired product should then increase.



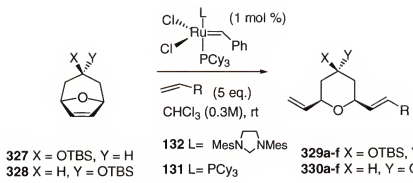
324a X = Y = O
324b X = OTBS, Y = H
324c X = H, Y = OTBS

325a X = Y = O
325b X = OTBS, Y = H
325c X = H, Y = OTBS

326a-c

Scheme 2-2. Reversibility of the ROM/CM reaction

As anticipated, the reactions involving silyl ether **327** reached completion within ten minutes (Scheme 2-3). No residual starting alkene could be observed by NMR. Furthermore, the introduction of the *tert*-butyldimethylsilyl group rendered the reaction irreversible. Upon exposure of the isolated ring-opened product **329a** to catalyst **132**, no ring closure was observed.

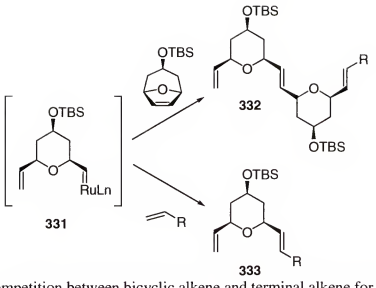


Scheme 2-3. ROM/CM of reduced derivatives

Table 2-2. ROM/CM of reduced derivatives

Pyran	Alkene	-R	Catalyst	Yield (%)
329a	Styrene	-Ph	**132**	60
329b	2-bromostyrene	-*o*-BrPh	**132**	18
329c	1-hexene	$-(CH_2)_3CH_3$	**131**	63
329d	allyl bromide	$-CH_2Br$	**132**	62
329e	4-bromo-1-butene	$-CHCH_2Br$	**132**	56
329f	Methylacrylate	$-CO_2Me$	**132**	0
330a	Styrene	-Ph	**132**	67
330b	1-hexene	$-(CH_2)_3CH_3$	**131**	75

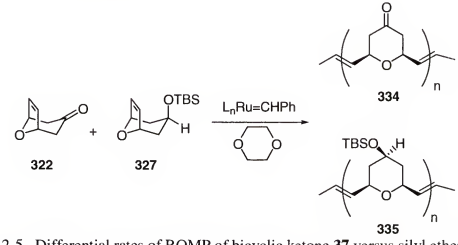
Quite surprisingly, however, the yields of the cross metathesis products were lower compared to reaction with the bicyclic ketone. This was attributed to the fact that the silyl ether was more reactive. Therefore, ROMP became a significant competing reaction and the bicyclic alkene competed with the donor alkene for the reactive intermediate (Scheme 2-4).



Scheme 2-4. Competition between bicyclic alkene and terminal alkene for reactive alkylidene

Consequently, the yield with styrene, which was, with bicyclic ketone **37**, in the high 80s, fell to the 60s with the more reactive silyl ether **327**. It was also noted that as the alkenes became less electron rich and therefore less reactive toward cross metathesis, ROMP became more favorable; thus the yield of the ring-opened cross metathesis product fell off dramatically as the suitability of the donor alkene to cross metathesis decreased. As seen in the case of 2-bromostyrene, the effect of a slight decrease in the reactivity of the alkene in the reaction with the bicyclic ketone seemed to be dramatically multiplied in the case of the bicyclic ether. Whereas the difference in the yield of the desired product of the reaction of the bicyclic ketone with styrene compared to the more hindered 2-bromostyrene was not even a mere 20%, the difference in the yields in the case of the bicyclic ether was a startling 42%. Moreover, while cross metathesis of the bicyclic ketone with methacrylate was modestly successful, no product could be observed in the reaction with ether **327**. The only reaction that seemed to be occurring in this case was ROMP, and significant amounts of oligomer **332** were isolated.

A competition experiment was conducted in order to establish the enhanced reactivity of ether **327** over ketone **37** caused by the conversion of an sp^2 to an sp^3 center (Scheme 2-5). Upon exposure of a mixture of the ketone and the ether to catalyst **132**, the reduced derivative was completely converted to oligomeric material within ten minutes whereas the ketone remained largely unreacted. Further studies with *exo*-silyl ether **328** showed that despite the absence of the large group in the axial position, the ether still displayed enhanced reactivity and was irreversible. The results of a competition experiment between the *exo*-silyl ether and the ketone were identical to those involving the *endo*-silyl ether. Based on these observations it appears that only the change in hybridization at C3, and not the position of the bulky silyl ether, was responsible for the change in reactivity.

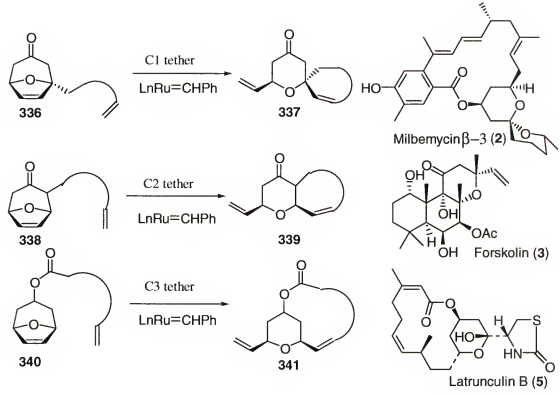


Scheme 2-5. Differential rates of ROMP of bicyclic ketone **37** versus silyl ether **327**

By tethering the donor alkene to the bicyclic olefin, the desired metathesis process was rendered intramolecular. The reaction could therefore be carried out at high dilution, promoting the desired coupling and negating the competing intermolecular oligomerization.

Domino Ring-Closing Metathesis/Ring-Opening Metathesis (RCM/ROM)

Placement of the tether at three different positions on the bicycle allows entry into a variety of fused pyran systems (Scheme 2-6). Attachment at C1 leads to the generation of spiro-fused bicyclic compounds **337**, which are common in many natural products such as milbemycin β-3 (**2**). A tethered donor olefin at C2 leads to linear-fused structures **339**, present in compounds such as forskolin (**3**). Bridged-fused bicycles **341**, such as are present in Latrunculin B (**5**), result from tethers at C3.

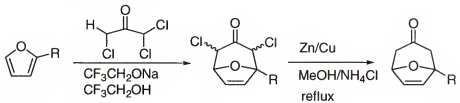


Scheme 2-6. Toward spiro-, linear-, and bridged-fused bicyclic systems

Toward Spiro-Fused Bicyclic Systems

Initial studies of the domino RCM/ROM reaction focused on the synthesis of spiro-fused systems from the C1-tethered intermediates. A series of oxabicyclo[3.2.1] octene derivatives **344a-d** with the donor olefin tethered at the bridgehead were prepared *via*

oxyallyl cation cycloaddition of 2-substituted furans **342a-d** under Föhlisch conditions[23] (Scheme 2-7). Compounds **342a-d** were synthesized by alkylation of 2-lithiated furan with the corresponding alkenyl halide.



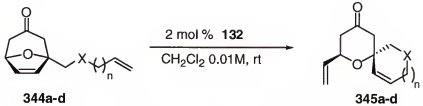
342a R = $(CH_2)_2CH{=}CH_2$
342b R = $(CH_2)_3CH{=}CH_2$
342c R = $CH_2OCH_2CH{=}CH_2$
342d R = $(CH_2)_4CH{=}CH_2$

343a-d

344a 69%[a]
344b 71%[a]
344c 88%[a]
344d 60%[a]

Scheme 2-7. Synthesis of C1-tethered intermediates. [a]Yields over two steps (**342-344**)

Dechlorination of the cycloadducts **343a-d** with zinc-copper couple afforded metathesis precursors **344a-d** in good yield. Upon exposure to 2 mol% of catalyst **132**, tandem RCM/ROM led to formation of the corresponding five and six-membered spirocycles **345a-c** in good yield (Scheme 2-8) (Table 2-3).



344a-d **345a-d**

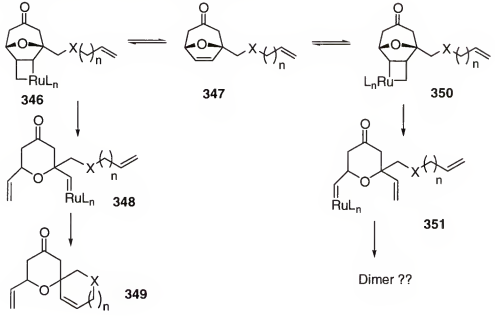
Scheme 2-8. Synthesis of spirocyclic pyran derivatives by domino RCM/ROM

Table 2-3. Synthesis of spirocyclic pyran derivatives by domino RCM/ROM
[a]Yield of recovered starting material [b]Yield of dimer isolated

Bicyclic ketone	X	n	Product	Yield (%)
344a	$-CH_2-$	0	**345a**	56 (16)[a]
344b	$-CH_2-$	1	**345b**	82 (10)[a]
344c	-O-	1	**345c**	80
344d	$-CH_2-$	2	**345d**	15 (44)[b]

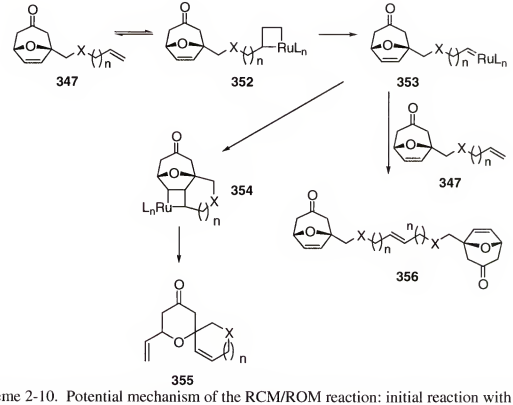
Attempts to promote efficient rearrangement to the seven-membered **345d** were unsuccessful. Dimerization of the terminal vinyl groups was observed, and much of the starting material was recovered unchanged. Neither increased catalyst loading nor elevated temperatures improved the yield of the reaction.

These rearrangement reactions raised some interesting mechanistic questions. Based on the systems under study, one of two major pathways could be in play. If the initial reaction occurred between the catalyst and the internal olefin, regiochemical issues would arise (Scheme 2-9). The intermediate alkylidene could form either on the carbon bearing the side chain (**348**) or on the less substituted carbon (**351**). The second metathesis reaction to effect ring closure would be more favorable if the terminal vinyl group and the alkylidene were on the same carbon.



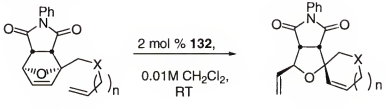
Scheme 2-9. Possible mechanism of the intramolecular RCM/ROM reaction: initial reaction with the internal olefin

Alternatively, if the initial metallocyclobutane involved the terminal olefin (**352**), attack of the tethered alkylidene would, in closing one ring, open the original bicyclic compound (Scheme 2-10). Control of regiochemistry would be governed by the intramolecular nature of the opening. Since the reactions, for the most part, were high yielding with the observation of few side products, the latter mechanism seemed probable. Furthermore, the isolation of 44% of dimer in the RCM/ROM attempt on the six-carbon-tethered **344d** indicated that the catalyst reacted initially with the terminal olefin. In the case of bicyclic octene **345d**, ring closure was unfavorable, so the reactive alkylidene **353** reacted with the terminal alkene of a second substrate molecule, forming the dimer.



Scheme 2-10. Potential mechanism of the RCM/ROM reaction: initial reaction with the terminal olefin

With these mechanistic considerations in mind, it was thought that increasing the reactivity of the internal olefin would promote the second metathesis process and discourage dimerization. The analogous oxabicyclo[3.2.1]heptene derivatives, were prepared by Diels-Alder reaction of furans **342a-d** with N-phenyl maleimide. Exposure to catalyst **132** promoted bond reorganization to the tricyclic compounds **358a-d** in good to excellent yields (Scheme 2-11) (Table 2-4). As expected, five and six-membered closures were most efficient. Interestingly, the formation of the seven-membered ring system **358d** proceeded significantly more smoothly in this series, perhaps due to the enhanced reactivity of the more highly strained oxabicyclo[2.2.1]heptene derivative. An increase in ring strain resulted in a decrease in the enthalpy of activation of the second metathesis reaction while the entropy of activation remained the same. The reaction, thus, became more favorable.



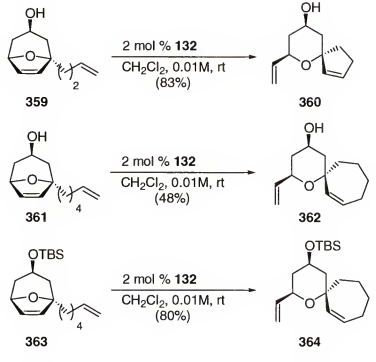
357a-d **358a-d**

Scheme 2-11. Synthesis of spirocyclic tetrahydrofuran derivatives by domino RCM/ROM

Table 2-4. Synthesis of spirocyclic tetrahydrofuran derivatives by domino RCM/ROM. [a]Yield of recovered starting material

[2.2.1] dienes	-X-	n	Product	Yield (%)
357a	$-CH_2-$	0	**358a**	84
357b	$-CH_2-$	1	**358b**	78
357c	-O-	1	**358c**	95
357d	$-CH_2-$	2	**358d**	54 (19)[a]

Based on previous knowledge that conversion of C3 from an sp^2 to an sp^3 center enhanced the reactivity of the bicyclic olefin, we proposed that the reduced derivatives of the previously studied metathesis precursors would be better suited to undergo the second metathesis process. The increased reactivity would be observed particularly in the case of the seven-membered closure where dimerization of the initial alkylidene was competitive with the slow intramolecular metathesis reaction. The reduced forms of dienes **344a** and **344d** were synthesized using L-selectride (Scheme 2-12). These five and seven-membered closures were examined since they were less efficient than the cyclohexyl closures. In the cyclopentyl case it may be somewhat difficult for the shorter tether to reach the bridged alkene while the seven may be slowed by non-bonded interactions in the tether.



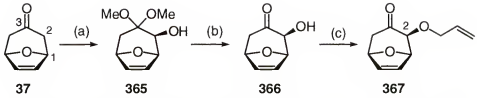
Scheme 2-12. Domino RCM/ROM with reduced derivatives

Reduction of ketone **344a** to the *endo*-alcohol **359** followed by rearrangement gave **360** in an improved 83% yield. The more difficult seven closure was also better with *endo*-alcohol **361**, with the yield tripling to 48%. Based on other studies being carried out in the Wright group, it was known that placement of a –TBS group at C3 enhanced the rate of the reactivity of the endocyclic olefin even more than the presence of the hydroxyl group in the same position. As predicted, silyl ether **363**, when exposed to catalyst **132** underwent the RCM/ROM reaction, delivering spiro-product **364** in 80% isolated yield.

Toward Linear-Fused Bicyclic Systems

Placement of an olefin tether at C2 on the bicyclic octene prepares the system for RCM/ROM to produce linear-fused pyrans. Two general types of tethers were examined. The first was attached to the bicycle via an oxygen atom. A methylene group acted as the second type of linker. In this case, tethers occupying both an *endo* and *exo* orientation at C2 were examined.

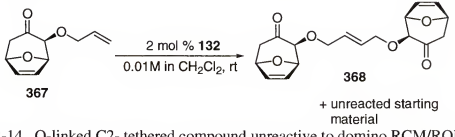
The *endo* oxygen-linked tethers were synthesized from 8-oxabicyclo[3.2.1]oct-6-en-3-one (Scheme 2-13). By a known procedure[115], diacetoxyiodobenzene in methanolic potassium hydroxide effected the introduction of an *endo*- hydroxyl group at C2, at the same time converting the ketone to the corresponding ketal. Acid hydrolysis afforded the α-hydroxy ketone **365**, which was then allylated under basic conditions to give C2-tethered intermediate **367** in 40% yield.



a) PhI(OAc)$_2$, KOH/MeOH (55%); b) 6M HCl, H_2O (90%); c) (i)K_2CO_3, DMF reflux, (ii) allylbromide (40%)

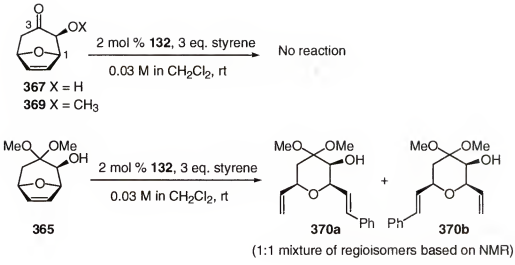
Scheme 2-13. Synthesis of C2-tethered intermediate

Upon exposure to 2 mol % of catalyst **132**, compound **367**, as a 0.01M solution in dichloromethane, exhibited no rearrangement to the RCM/ROM product. After more than 48 hours, starting material was recovered unchanged. The only new product observed was that resulting from dimerization of **367** (Scheme 2-14).



Scheme 2-14. O-linked C2- tethered compound unreactive to domino RCM/ROM

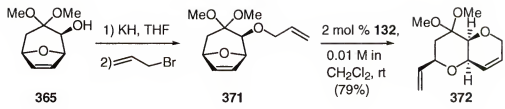
Upon comparison to the highly successful C1-tethered systems, and considering the unusual effects of the remote substituent at C3 on the rate of reactivity of the internal olefin towards metathesis, it was hypothesized that the presence of an oxygen atom directly bonded to the bicycle exerted some sort of deactivating influence. Attempts to elicit the more basic ROM/CM with styrene were unsuccessful (Scheme 2-15). In the presence of 2 mol% of catalyst **132** and three equivalents of styrene as a 0.3M solution in dichloromethane, no reaction was detected. Starting material remained unchanged.


2 mol % 132, 3 eq. styrene
0.03 M in CH2Cl2, rt
No reaction
367 X = H
369 X = CH3
2 mol % 132, 3 eq. styrene
0.03 M in CH2Cl2, rt
365
370a
370b
(1:1 mixture of regioisomers based on NMR)

Scheme 2-15. C2-substitutent effects on reactivity of endocyclic olefin

Drawing on the previous knowledge that conversion of C3 from an sp^2 to an sp^3 center enhanced the reactivity of the endocyclic olefin, the α-hydroxy ketal isolated after treatment with diacetoxyiodobenzene was examined for activity in the ROM/CM with styrene. Not surprisingly, this compound underwent ROM/CM in the presence of 2 mol% of catalyst **132** and three equivalents of styrene. The reaction was complete within 30 minutes; however, a one to one mixture of regioisomers was obtained (Scheme 2-15).

The problem of regioselectivity should then be overcome in the case of the intramolecular reaction based on the mechanism of initial attack on the terminal olefin. Accordingly, the allyl tether was attached to α-hydroxy ketal **365**, generating the reduced C2-tethered intermediate **371** in 45% yield (Scheme 2-16). As predicted, treatment of **371** with catalyst **132** afforded the RCM/ROM product **372** in 79% yield. The reaction was complete within one hour and no dimer was isolated after column chromatography.



365 371 372

Scheme 2-16. Domino RCM/ROM of C2-tethered intermediate

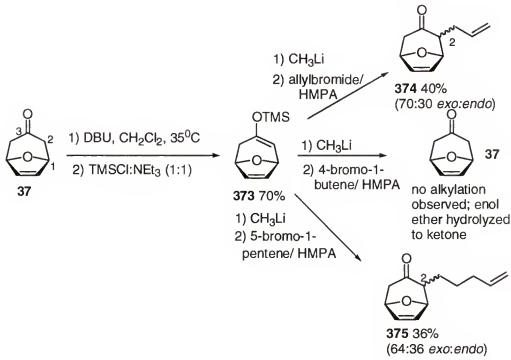
In the studies of the C1-substituted ketones, formation of six-membered rings by the domino RCM/ROM process occurred smoothly, giving high yields of 6,6- and 5,6-spiro-fused products. Although the system was slightly altered, with the tether moved from C1 to C2, it was expected that cyclization to form the 6,6-linear fused system would be similarly successful. As it was necessary to change the hybridization at C3 from sp^2 to sp^3 to induce the desired RCM/ROM, it was proposed that the presence of an oxygen atom directly bonded to the bicyclic system at C2 exhibited a deactivating effect, rendering the endocyclic alkene unreactive. An attempt was made to eliminate this effect by replacing the oxygen in the 4-atom tether with carbon. If the presence of oxygen at C2 was responsible for the diminished reactivity of the system, replacement with carbon should then allow successful RCM/ROM to form the 6,6-linear-fused system without changing the hybridization at C3. The synthesis of the all-carbon tether highlighted the issue of the relevance of stereochemistry at C2. Could rearrangement occur as readily with a tether in the *exo* position as with one in the *endo* position? Assuming that the system reacted by a RCM/ROM process, models of both types indicated that the *endo* tether was favorably aligned for the [2+2] cycloaddition while the tether in the *exo* position appeared unable to line up with the bicyclic olefin, lying far from the internal double bond.

In order to study both the *endo* and *exo* systems, Mann's method[116] for alkylation of the TMS enol ether of 8-oxabicyclo[3.2.1]oct-6-en-3-one was altered slightly. When carried out at -78°C and maintained below 0°C until quenched, the reaction, according to Mann, gives solely the *exo* isomer in a yield of 75%. If the reaction was instead allowed to come to room temperature, mixtures of both *endo* and *exo* isomers were obtained.

Attempts to synthesize the *endo* and *exo* butenyl-substituted bicyclic ketones using the variation on Mann's alkylation procedure as well as the original conditions were unsuccessful. Only hydrolysis of the enol ether to produce oxabicyclic ketone **37** was observed (Scheme 2-17). This α-butenyl substituted derivative would have been helpful in supporting a possible C2 effect as it would have introduced only a single variable, that is, replacement of oxygen by carbon. Both the length of the chain and the stereochemistry of the tether would have remained unchanged.

Nonetheless, *endo* and *exo* isomers containing both five- and three-carbon chain lengths were synthesized (Scheme 2-17). Ratios of *exo*:*endo* isomer were determined by GC/MS. With both the *endo* and *exo* isomers of each system in hand, albeit as mixtures, it was possible to investigate the effect of stereochemistry on the domino RCM/ROM process. A model of the 5-carbon-tethered intermediate suggested, as expected, that only a tether in the *endo* position would be favorably aligned for RCM/ROM with the bicyclic alkene. The *exo* isomer should then remain unchanged or undergo dimerization. Upon exposure of a 64:36 (*exo*:*endo*) mixture of **375** to 2 mol% of catalyst **132** in dichloromethane at a concentration of 0.01M at room temperature for 72 hours, no visible

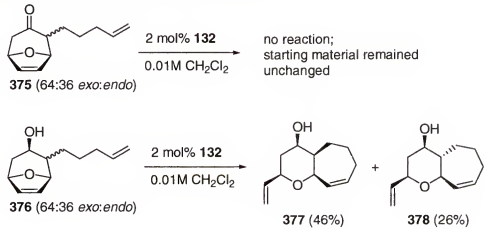
reaction was observed (Scheme 2-18). Starting material was recovered unchanged.



Scheme 2-17. Synthesis of C2-carbon tethered intermediates

By comparison to the studies of the spiro-fused systems, this result was not highly unexpected. In the case of the C1-substituted derivative **344d** (Scheme 2-8) that would lead to a 6,7-spiro fused bicycle, no significant RCM/ROM product was observed. Formation of the seven-membered ring was rather difficult, and only when the system was made more reactive by conversion of C3 from an sp^2 to an sp^3 center did the domino RCM/ROM process occur. Compound **375** would similarly rearrange to a 6,7-linear fused bicycle. The mixture of **375** was therefore reduced to the *endo* alcohol using L-selectride. Upon exposure of the 64:36 (*exo*:*endo*) mixture of alcohols **376** to the same conditions used with **375**, starting material was completely consumed within two hours, and two isomeric rearranged metathesis products were obtained (Scheme 2-18). The 6,7-linear-*cis*-fused product **377** resulted from the domino metathesis of the intermediate with

the tether in the *endo* position. The 6,7-linear-*trans*-fused product **378** was formed by domino metathesis of the *exo*-tethered derivative.



Scheme 2-18. RCM/ROM of 2-pentenyl-8-oxabicyclo[3.2.1]octene derivatives

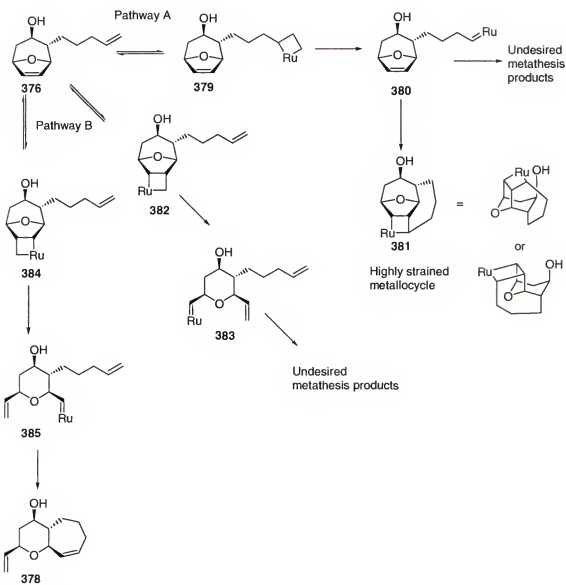
Based on the starting ratios of *exo* to *endo* isomer, the *cis*-fused product was isolated in 46% yield, a yield comparable to that observed in the reduced 6,7-spiro-fused product **362** (Scheme 2-12). Only 26% of the *trans*-fused product was obtained. GC/MS data of the crude product mixture revealed several compounds of mass greater than 300, suggesting the presence of oligomers, though none were isolated after column chromatography.

The isolation of *trans*-fused product warranted closer consideration of the stereochemical issues of the C2-tether. It appeared, based on models, that the *exo*-C2-tethered system could not undergo RCM/ROM; therefore, formation of the *trans*-fused product suggested one of two scenarios. Possibly the strain associated with reaction of the endocyclic alkene with the terminal alkylidene, formed by attack of the catalyst on the terminal olefin, was not significant enough to prevent the reaction. On the other hand, it is possible that the change in hybridization at C3 from sp^2 to sp^3 significantly

increased the reactivity of the internal olefin such that it became competitive with the terminal double bond for initial loading of the catalyst. This would then suggest the interference of an alternate pathway (B), a ROM/RCM rather than the RCM/ROM believed to be in play in the case of the C1-substituted systems. By this pathway, the first metathesis process would take place at the internal olefin, leading to one of two reactive intermediates (Scheme 2-19). If, in fact, the two alkenes in the system were competing for catalyst, three different alkylidene intermediates could potentially form. If the strain resulting in the second metallocyclobutane formation was too great, any alkylidene formed on the terminal olefin (**380**) would lead to oligomerization, dimerization or other undesired reactions. Based on the reaction of the α-hydroxy ketal **365** with styrene (Scheme 2-15), the regioselectivity of ROM of the internal olefin would be low to nonexistent, so the probability of formation of alkylidenes **383** and **385** would be similar. As in the scenario depicted for the C1-substituted compounds, only the alkylidene formed in close proximity to the alkenyl tether (**385**) should result in RCM. The other alkylidene might lead to oligomers and other undesired metathesis products.

This might explain the very low yield of the *trans*-fused product and the moderate yield of the *cis*-fused bicycle. Should the alternative pathway (B) account for the reactivity of the reduced derivatives, that is derivatives with an alcohol or silyl ether at C3, loading of the catalyst onto the terminal olefin in a competitive situation would only lead to product in the case of the *endo*-tethered compounds. One could therefore expect no more than 50% yield with the *exo* precursors, due to the lack of selectivity in the ROM of the internal olefin, and possibly far less depending on the relative reactivity of the

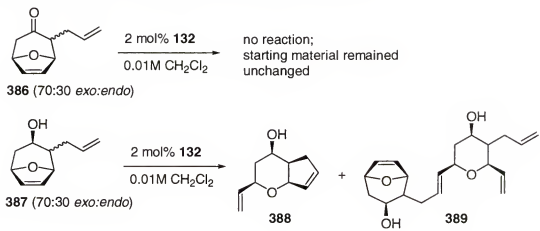
internal and terminal alkenes. The *endo* precursors, on the other hand, might give a higher yield since two of the three possible alkylidenes could lead to product.



Scheme 2-19. Alternate mechanism leading to domino ROM/RCM in the synthesis of 6,7-linear-*trans*-fused bicycles

More evidence for the involvement of this alternate pathway was obtained with the 3-carbon-tethered systems **386**. These tethers, based on models, would be expected to be too short for favorable formation of a metallocyclobutane intermediate with the internal

alkene if the catalyst first loaded onto the terminal olefin. If it formed, it would be highly strained. Exposure of a 70:30 *exo:endo* mixture of isomers to 2 mol% catalyst **132** in dichloromethane at a concentration of 0.01M at room temperature resulted in no visible reaction (Scheme 2-20). Starting material remained unchanged. When the mixture was reduced with L-selectride and the resulting 70:30 mixture of alcohols subjected to the same conditions, all the starting material was consumed within one hour. Only the 6,5-linear-*cis*-fused product resulting from the *endo* precursor was isolated (38%). Though no 6,5-linear-*trans*-fused bicycle was isolated, this was not unusual since that system is thermodynamically unstable. A white solid was also obtained. Mass spectrometry analysis indicated the presence of a molecule of mass 332 that corresponds to compound **389**. This implies the involvement of the alternate pathway.



Scheme 2-20. RCM/ROM of 2-allyl-8-oxabicyclo[3.2.1]octene derivatives

Though it is not out of the question to imagine the possibility that initial loading of catalyst on the terminal alkene could lead to the observed product **388**, it is also possible that the initial metathesis process indeed occurs on the internal olefin following the alternative pathway earlier described. Again, the 4-carbon-*exo*-tethered precursor would have been an interesting case to examine. Since, in the *exo* position, the

metallocyclobutane intermediate formed between the terminal alkylidene and internal olefin (pathway A) would be highly strained, the possibility of two pathways exists. If the rearrangement occurred in high yields as would be expected with a closure of a six-membered ring, one would have to conclude that pathway A was dominant. On the other hand, low yields would suggest a preference for pathway B.

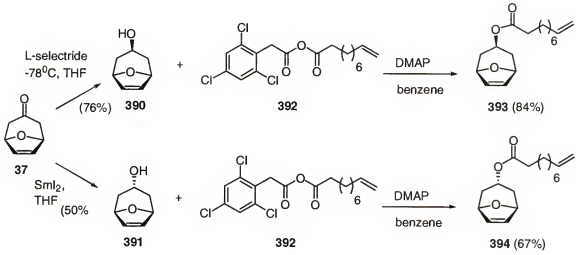
Without these results, it is difficult to conclude which pathway is operating in the metathesis of these systems. It appears that the ketone derivatives in both the spiro- and linear-fused studies follow pathway A. In the case of the reduced C1-substituted derivatives, high yields of rearranged product suggest the opearation of pathway A. Yet, it is possible, as evidenced by studies carried out by Plummet and Arjona on norbornene systems[92] and by studies perfomed by M. Estrella in the Wright research group, that the presence of a substitutent at C1 results in high regioselectivity for formation of the alkylidene on the more substituted side, favoring subsequent ring closure.

In the case of the reduced C2-tethered precursors, it is possible that pathway A is in operation since indication of strain was based solely on models. Studies with the 3-carbon substituted system do, however, strongly suggest the possibility that the alternate pathway could be in operation.

Toward Bridged-Fused Bicyclic Systems

In the approach toward the bridged-fused bicycles, attachment of the tether at C3 resulted in conversion of C3 from an sp^2 to an sp^3 center and, essentially, an increase in the reactivity of the system; therefore, it was expected that the precursors would undergo the domino metathesis to yield the desired rearranged products. Two systems were investigated. The *exo* alcohol **391** was synthesized via samarium diiodide reduction of the bicyclic ketone **37** (Scheme 2-21). The *endo* alcohol **390** was achieved by reduction

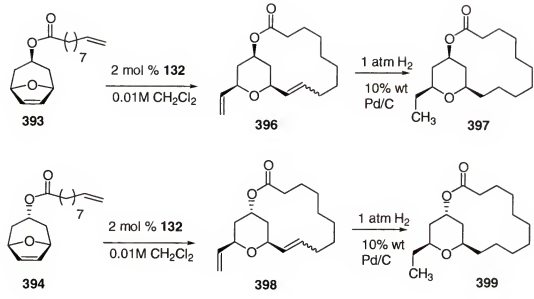
of **37** with L-selectride. A 10-carbon tether was attached to each alcohol via an esterification procedure involving an intermediate anhydride formed from 9-decenoic acid and 2,4,6-trichlorobenzoyl chloride.



Compound **392** was synthesized from 9-decenoic acid and 2,4,6-trichlorobenzoyl chloride in the presence of triethylamine in THF

Scheme 2-21. Synthesis of the C3-tethered metathesis precursors

Upon exposure to 2 mol% catalyst **132** in dichloromethane at a concentration of 0.01M at room temperature, each C3-substituted precursor underwent a domino RCM/ROM process to yield the bridged-fused bicyclic products (Scheme 2-22). As was expected with the formation of macrocycles by ring-closing metathesis, a mixture of *cis:trans* isomers was produced. Crude yields were relatively high, 70% and 76% for compounds **396** and **398** respectively. Hydrogenation of both crude mixtures yielded the saturated bridged-fused systems. Surprisingly, yields of the saturated products were low (less than 40%), yet oligomers or other byproducts were neither observed in the crude NMR nor isolated after column chromatography. It is possible that the loss occurred in the hydrogenation.



Scheme 2-22. RCM/ROM of C3-tethered intermediates

CHAPTER 3
CONCLUSIONS AND FUTURE WORK

Methodology for the synthesis of pyrans has been developed. Taking advantage of the intermolecular ring opening metathesis/cross metathesis (ROM/CM) reaction of 8-oxabicyclo[3.2.1]octene derivatives, it was possible to approach the *cis*-2,6-disubstituted pyran moiety present in a wide range of natural products. The reactivity of the system could be carefully tuned by controlling the hybridization at C3 on the bicycle. The rate of the reaction was slowed by the presence of a ketone at C3 and increased by replacement of the ketone by an alcohol or silyl ether. Preliminary work has begun on application of the methodology to the synthesis of Latrunculin B and Leucascandrolide A. One of the main challenges lies in designing an asymmetric approach to each molecule. The hope is to achieve the ROM/CM enantioselectively using either Grubbs' or Schrock's asymmetric metathesis catalysts. Recent literature has reported the success of these catalysts in promoting the asymmetric ring opening metathesis/cross metathesis (AROM/CM) of bicyclic ethers in high yield and good enantiomeric excess. Failing asymmetric metathesis, enzymatic desymmetrization or resolution could be investigated as an alternative to achieving enantioselectivity.

We have extended the methodology to the synthesis of spiro-, linear- and bridged-fused pyrans. Spiro-fused tetrahydrofuran derivatives were also achieved. Successful synthesis of 6,5-, 6,6- and 6,7- as well as 5,5-, 5,6- and 5,7- spiro-fused bicycles highlighted the ability to enhance reactivity by altering hybridization at C3 in the case of the [3.2.1]oxabicyclic systems and by manipulating enthalpic factors such as ring strain

in the case of the [2.2.1] systems. The spiro systems are ideal for the development of libraries of compounds. Not only do they provide a rigid framework, but also the substitution of an all carbon spirocyclic junction for the ketal moiety present in many natural products eliminates the instability associated with ketals. Furthermore, the spirocyclic derivatives consist of a range of handles for further functionalization and thus represent ideal substrates for combinatorial chemistry. It would be beneficial to investigate the synthesis of enantiomerically pure spirocyclic, perhaps taking advantage of the asymmetric [4+3] cycloaddition reaction to achieve asymmetry early in the synthesis.

A variety of linear-fused systems were successfully synthesized via a domino metathesis rearrangement, though the preparation of the metathesis precursors must be optimized if these reactions are to be considered synthetically useful. Further studies could be performed to better understand the mechanism of the rearrangement . In terms of enantioselectivity, synthesis of the alkenyl-substituted derivatives could involve the asymmetric enol ether of the oxabicyclic octene precursors.

Bridged-fused bicycles were also successfully synthesized. Such macrocycles are abundant in nature and could prove useful in the synthesis of libraries.

Clearly, the methodology has a wide range of uses. The intermolecular variant, in particular, yields pyran substructures that could serve as important intermediates in natural product synthesis. In addition, relatively complex systems are achieved in a single operation from readily available starting materials. Furthermore, the potential for introducing asymmetry in the methodology is high.

CHAPTER 4
EXPERIMENTAL PROCEDURES

General procedures. Reactions were carried out under an argon atmosphere. $CHCl_3$ was dried on basic alumina. Glassware was dried by either flaming under vacuum or storing in a 140°C oven for a minimum of 24 hours. Olefin metathesis catalysts were purchased from Strem Chemicals. Catalyst solutions were prepared by weighing the appropriate amount of catalyst into a clean, dry vial under an atmosphere of nitrogen, then adding the appropriate volume of dry chloroform. Thin-layer chromatography was performed using silica gel 60 F_{254} precoated plates (250 μm thickness). Column chromatography was performed using 230-400 mesh silica gel 60. NMR spectra were obtained on a Varian GEMINI2000 or Varian INOVA500 spectrophotometer using TMS as an internal reference. IR spectra were obtained as thin films between NaCl plates on a Perkin Elmer Spectrum One FT-IR spectrometer. The UFL Mass Spectroscopy Services performed high-resolution mass spectroscopy.

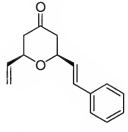


Figure 4-1. *cis*-[2-(*E*-2-phenylethenyl)-6-ethenyl] tetrahydropyran-4-one (**323a**)

Oxabicyclic ketone **322** (0.5g, 4mmol) and styrene (2.29 mL, 20 mmol) were dissolved in chloroform (10.2 mL). A solution of **132** (0.034g, 0.04 mmol) in chloroform (1 mL) was added and the resulting solution allowed to stir under argon at room

temperature. The reaction was monitored by NMR. Evaporation under reduced pressure and purification of the residue by silica gel chromatography using gradient elution (9:1 to 3:1, hexane:ethyl acetate) gave **323a** as a white solid; mp =145-148°C; (0.76g, 83%). R_f=0.27 (9:1, hexane:ethyl acetate). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.42-7.24 (5H, m), 6.68 (1H, d, J=15.7Hz), 6.30 (1H, dd, 15.7 Hz, 6.3 Hz), 5.97 (1H, ddd, J=17.3 Hz, 11.0 Hz, 6.0 Hz), 5.37 (1H, d, J=17.3 Hz), 5.25 (1H, d, 11.0 Hz), 4.45-4.32 (2H, m), 2.58-2.48 (4H, m). ^{13}C NMR (300MHz, $CDCl_3$): δ 206.0, 137.1, 136.3, 132.0, 128.8, 128.3, 128.1, 126.8, 116.8, 77.6, 77.5, 48.0, 47.5. HRMS (EI) calcd for $C_{15}H_{16}O_2$ $[M]^+$ 228.1150, found 228.1133. IR (film): 3025, 2965, 2906, 2872, 1710, 980, 969, 748 cm^{-1}.

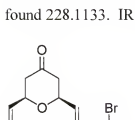


Figure 4-2. *cis*-{2-[*E*-2-(2-Bromo-phenyl)-ethenyl]-6-ethenyl} tetrahydropyran-4-one (**323b**)

Oxabicyclic ketone **322** (0.1g, 0.81mmol) and 2-bromostyrene (0.52 mL, 4.03 mmol) were dissolved in chloroform (2.0 mL). A solution of **132** (6.9 mg, 0.008 mmol) in chloroform (0.69 mL) was added and the resulting solution allowed to stir under argon at room temperature. The reaction was monitored by NMR. Evaporation under reduced pressure and purification of the residue by silica gel chromatography using gradient elution (10:0 to 9:1, hexane:ethyl acetate) gave **323b** as a yellow oil (0.16g, 65%); R_f=0.46 (6:4, hexane:ethyl acetate). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.57-7.10 (4H, m), 7.02 (1H, d, J=15.7 Hz), 6.22 (1H, dd, J=15.7 Hz, 6.0 Hz), 5.97 (1H, ddd, J=17.0 Hz, 10.5 Hz, 5.4 Hz), 5.38 (1H, d, 17.0 Hz), 5.25 (1H, d, 10.5 Hz), 4.44-4.36 (1H, m), 4.27-

4.21 (1H, m), 2.60-2.40 (4H, m). ^{13}C NMR (300MHz, $CDCl_3$): δ 206.1, 137.0, 136.2, 133.2, 131.0, 130.9, 130.6, 129.5, 127.7, 127.3, 116.8, 76.8, 60.6, 47.8, 47.5. HRMS (EI) calcd for $C_{15}H_{15}O_2Br$ $[M]^+$ 306.0255, found 306.0163. IR (film): 2927, 1722, 1467, 1025, 966, 752 cm^{-1}.

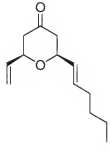


Figure 4-3. *cis*-[2-(*E*-Hex-1-enyl)-6-ethenyl] tetrahydropyran-4-one (**323c**)

Oxabicyclic ketone **322** (0.25g, 2mmol) and 1-hexene (1.26 mL, 10 mmol) were dissolved in chloroform (6 mL). A solution of **131** (0.017g, 0.02 mmol) in chloroform (0.72 mL) was added and the resulting solution allowed to stir under argon at room temperature. The reaction was monitored by NMR. Evaporation under reduced pressure and purification of the residue by silica gel chromatography using gradient elution (9.5:0.5 to 9:1, hexane:ethyl acetate) gave **323c** as a colorless oil (0.37g, 89%). R_f = 0.38 (3:1, hexane:ethyl acetate). ^1H NMR (300 MHz, $CDCl_3$): δ 5.94 (1H, ddd, J=17.2 Hz, 10.7 Hz, 5.8 Hz), 5.74 (1H, dt, J=15.5 Hz, 6.7 Hz), 5.55 (1H, dd, J=15.5 Hz, 6.4 Hz), 5.32 (1H, d, J=17.2 Hz), 5.21 (1H, d, J=10.7 Hz), 4.15-4.09 (2H, m), 2.46-2.33 (4H, m), 2.09-2.03 (2H, m), 1.39-1.26 (4H, m), 0.89 (3H, t, J=7 Hz). ^{13}C NMR (300MHz, $CDCl_3$): δ 206.6, 137.3, 134.1, 129.0, 116.6, 77.5, 48.1, 47.5, 32.1, 31.2, 22.4, 14.1; HRMS (EI) calcd for $C_{13}H_{20}O_2$ $[M]^+$ 208.1463, found 208.1416. IR (film): 2959, 2928, 2858, 1722, 1057, 970, 928 cm^{-1}.

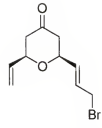


Figure 4-4. *cis*-[2-(*E*-3-Bromo-propenyl)-6-ethenyl] tetrahydropyran-4-one (**323d**)

Oxabicyclic ketone **322** (0.5g, 4mmol) and allyl bromide (1.73 mL, 20 mmol) were dissolved in chloroform (10.2 mL). A solution of **132** (0.034g, 0.04 mmol) in chloroform (1 mL) was added and the resulting solution allowed to stir under argon at room temperature. The reaction was monitored by NMR. Evaporation under reduced pressure and purification of the residue by silica gel chromatography (9:1, hexane:ethyl acetate) gave **323d** as a pale yellow oil (0.70g, 71%); R_f=0.61 (6:4, hexane:ethyl acetate). ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.07-5.81(3H, m), 5.34 (1H, d, J=17.3 Hz), 5.23 (1H, d, J=10.8Hz), 4.24-4.16 (2H, m), 3.96 (2H, d, J=7.1 Hz), 2.49-2.33 (4H, m). ^{13}C NMR (300 MHz, $CDCl_3$): δ 205.6, 136.9, 133.6, 128.2, 116.8, 77.5, 76.0, 47.4, 47.3, 31.6. HRMS (EI) calcd for $C_{10}H_{13}BrO_2$ $[M]^+$ 244.0099, found 244.0090. IR (film): 2967, 2903, 2846, 1721, 1333, 1252, 1057, 967, 932 cm^{-1}.

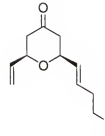


Figure 4-5. *cis*-[2-(*E*-4-Bromo-but-1-enyl)-6-ethenyl] tetrahydropyran-4-one (**323e**)

Oxabicyclic ketone **322** (0.25g, 2mmol) and 4-bromo-1-butene (1.02 mL, 10 mmol) were dissolved in chloroform (6 mL). A solution of **132** (0.017g, 0.02 mmol) in chloroform (0.72 mL) was added and the resulting solution allowed to stir under argon at room temperature. The reaction was monitored by NMR. Evaporation under reduced pressure and purification of the residue by silica gel chromatography using gradient elution (9.5:0.5 to 9:1, hexane:ethyl acetate) gave **323e** as a pale yellow oil (0.37g, 72%); R_f= 0.68 (6:4, hexane:ethyl acetate). ^{1}H NMR (300 MHz, $CDCl_3$): δ5.93 (1H, ddd, J=17.3 Hz, 10.5 Hz, 5.62 Hz), 5.82-5.64 (2H, m), 5.33 (1H, dd, J=17.3 Hz, 1.22 Hz), 5.23 (1H, dd, J=10.5 Hz, 1.22 Hz), 4.20-4.13 (2H, m), 3.41 (2H, t, J=6.84 Hz), 2.67-2.60 (2H, m), 2.48-2.35 (4H, m). ^{13}C NMR (300 MHz, $CDCl_3$): δ 206.1, 137.1, 132.1, 129.6, 116.8, 77.5, 77.0, 47.8, 47.4, 35.6, 31.9. HRMS (LSIMS) calcd for $C_{11}H_{16}O_2Br$ $[M+H]^+$ 259.0333, found 259.0398. IR (film): 2966, 2903, 2854, 1722, 1331, 1257, 1055, 971, 932 cm^{-1}.

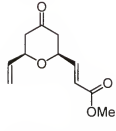


Figure 4-6. *cis*-2-[*E*-(2-carbomethoxyethenyl)-6-ethenyl] tetrahydropyran-4-one (**323f**)

Oxabicyclic ketone **322** (0.25g, 2mmol) and methacrylate (0.91 mL, 10 mmol) were dissolved in chloroform (6 mL). A solution of **132** (0.017g, 0.02 mmol) in chloroform (0.72 mL) was added and the resulting solution allowed to stir under argon at room temperature. The reaction was monitored by NMR. Evaporation under reduced pressure and purification of the residue by silica gel chromatography (3:1, hexane:ethyl acetate) gave **323f** as a pale yellow oil (0.14g, 33%); R_f= 0.67 (6:4, hexane:ethyl acetate).

^{1}H NMR (300 MHz, $CDCl_3$): δ 6.92 (1H, dd, J=15.8 Hz, 4.2 Hz), 6.17 (1H, d, J=15.8 Hz), 5.93 (1H, ddd, J=17.2 Hz,10.5 Hz, 5.3 Hz), 5.36(1H, d, J=17.2 Hz), 5.25 (1H, d, 10.5 Hz), 4.38-4.34 (1H, m), 4.25- 4.18 (1H, m), 3.77 (3H, s), 2.55-2.32 (4H, m). ^{13}C NMR (300MHz, $CDCl_3$): δ 205.1, 166.7, 145.3, 136.7, 121.2, 116.7, 77.4, 75.1, 52.0, 47.3, 46.6. HRMS (EI) calcd for $C_{11}H_{14}O_4$ $[M]^+$ 210.0892, found 210.0941. IR (film): 2955, 2852, 1724, 1316, 1165, 991, 775 cm^{-1}.

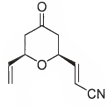


Figure 4-7. *cis*-2-[*E*-(2-cyanoethenyl)-6-ethenyl] tetrahydropyran-4-one (**323g**)

Oxabicyclic ketone **322** (0.25g, 2mmol) and acrylonitrile (0.66 mL, 10 mmol) were dissolved in chloroform (6 mL). A solution of **132** (0.017g, 0.02 mmol) in chloroform (0.72 mL) was added and the resulting solution allowed to stir under argon at room temperature. The reaction was monitored by NMR. Evaporation under reduced pressure and purification of the residue by silica gel chromatography (3:1, hexane:ethyl acetate) gave **323g** as a pale yellow oil (0.034g, 10%); R_f= 0.50 (6:4, hexane:ethyl acetate). ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.68 (1H, dd, J=16.4 Hz, 3.5 Hz), 5.92 (1H, ddd, J= 16.9 Hz, 10.5 Hz, 5.6 Hz), 5.8 (1H, d, J=16.4 Hz), 5.35 (1H, d, J=16.9 Hz), 5.26 (1H, d, J=10.5 Hz), 4.37-4.33 (1H, m), 4.23-4.20 (1H, m), 2.55-2.28 (4H, m). ^{13}C NMR (300MHz, $CDCl_3$): δ 204.0, 151.1, 136.3, 117.1, 112.3, 100.6, 77.6, 74.7, 47.2, 46.2. HRMS (EI) calcd for $C_{10}H_{11}O_2N$ $[M]^+$ 177.0790, found 177.0813. IR (film): 2955, 2852, 1723, 1282, 1174, 1057, 980, 933 cm^{-1}.

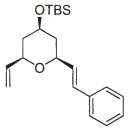


Figure 4-8. *cis*-4-*tert*-Butyldimethylsilyloxy-*cis*-[2-(*E*-2-phenylethenyl)-6-ethenyl] tetrahydropyran (**329a**)

Oxabicyclic ether **327** (0.25g, 1.04mmol) and styrene (0.6 mL, 5.2 mmol) were dissolved in chloroform (3 mL). A solution of **132** (8.9 mg, 0.01 mmol) in chloroform (0.5 mL) was added and the resulting solution allowed to stir under argon at room temperature. The reaction was monitored by NMR. Evaporation under reduced pressure and purification of the residue by silica gel chromatography using gradient elution (10:0 to 9.5:0.5, hexane:ethyl acetate) gave **329a** as a colorless oil (0.22g, 60%); R_f=0.43 (9.5:0.5, hexane:ethyl acetate). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.31-7.13 (5H, m), 6.54 (1H, d, J=15.9 Hz), 6.15 (1H, dd, J=15.9 Hz, 6.1 Hz), 5.83 (1H, ddd, J=17.3 Hz, 10.5 Hz, 5.9 Hz), 5.22 (1H, dd, J=17.3 Hz, 1.5 Hz), 5.06 (1H, dd, J=10.5 Hz, 1.5 Hz), 4.00-3.94 (1H, m), 3.87-3.76 (2H, m), 1.90-1.79 (2H, m), 1.42-1.24 (2H, m), 0.81 (9H, s), 0.00 (6H, s). ^{13}C NMR (300 MHz, $CDCl_3$): δ 138.6, 137.0, 130.7, 129.9, 128.7, 127.8, 126.7, 115.6, 76.6, 76.4, 68.8, 41.8, 41.4, 26.0, 18.3, -4.3. HRMS (CI) calcd for $C_{21}H_{33}O_2Si$ $[M+H]^+$ 345.2250, found 345.2200. IR (film): 2952, 2929, 2886, 2857, 1253, 1075, 837, 775 cm^{-1}.

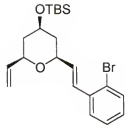


Figure 4-9. *cis-4-tert*-Butyldimethylsilyloxy-*cis*-{2-[*E*-2-(2-bromo-phenyl)-ethenyl]-6-ethenyl} tetrahydropyran (**329b**)

Oxabicyclic ether **327** (0.25g, 1.04mmol) and 2-bromostyrene (0.68 mL, 5.2 mmol) were dissolved in chloroform (3 mL). A solution of **132** (8.9 mg, 0.01 mmol) in chloroform (0.5 mL) was added and the resulting solution allowed to stir under argon at room temperature. The reaction was monitored by NMR. Evaporation under reduced pressure and purification of the residue by silica gel chromatography using gradient elution (10:0 to 9.5:0.5, hexane:ethyl acetate) gave **329b** as a yellow oil (0.08 g, 18%); R_f=0.39 (9.5:0.5, hexane:ethyl acetate). ^{1}H NMR (300 MHz, $CDCl_3$): δ7.54 -7.05 (4H, m), 6.97 (1H d, J=16.0 Hz), 6.2 (1H, dd, J=16.0 Hz, 6.23 Hz), 5.92 (1H, ddd, J=17.3 Hz, 10.5 Hz, 5.4 Hz), 5.32 (1H, d, J=17.3Hz), 5.15 (1H, d, J=10.5 Hz), 4.14-4.08 (1H, m), 3.97- 3.86 (2H, m), 2.04-1.87 (2H, m), 1.57-1.33 (2H, m), 0.90 (9H, s), 0.10 (6H, s). ^{13}C NMR (300 MHz, $CDCl_3$): δ 138.5, 136.8, 133.1, 132.8, 129.5, 129.0, 127.6, 127.2, 124.0, 115.5, 76.5, 76.3, 68.7, 41.7, 41.4, 26.0, 18.3, -4.3. HRMS (EI) calcd for $C_{21}H_{31}O_2$ Si Br O_2 $[M]^+$ 422.1277, found 422.1289. IR (film): 2952, 2928, 2856, 1470, 1254, 1116, 1077, 1025, 964, 914, 837, 776, 749, 670 cm^{-1}.

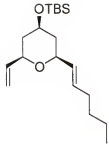


Figure 4-10. *cis-4-tert*-Butyldimethylsilyloxy-*cis*-[2-(*E*-hex-1-enyl)-6-ethenyl] tetrahydropyran (**329c**)

Oxabicyclic ether **327** (0.15g, 0.64 mmol) and 1-hexene (1.99 mL, 15.9 mmol) were dissolved in chloroform (0.034 mL). A solution of **131** (5.4 mg, 0.006 mmol) in chloroform (0.1 mL) was added and the resulting solution allowed to stir under argon at room temperature. The reaction was monitored by NMR. Evaporation under reduced pressure and purification of the residue by silica gel chromatography using gradient elution (10:0 to 9.5:0.5, hexane:ethyl acetate) gave **329c** as a colorless oil (0.13 g, 63%); R_f=0.43 (9.5:0.5, hexane:ethyl acetate). ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.89 (1H, ddd, J=17.3 Hz, 10.5 Hz, 5.8 Hz), 5.70 (1H, dt, J=15.6 Hz, 6.5 Hz), 5.51 (1H, dd, J=15.4 Hz, 6.4 Hz), 5.26 (1H, d, J=17.3 Hz), 5.12 (1H, d, J=10.5 Hz), 3.89-3.80 (3H, m) 2.07-2.00 (2H, m), 1.87-1.83 (2H, m), 1.41-1.28 (6H, m), 0.90 (12H, m), 0.08 (6H, s). ^{13}C NMR (300 MHz, $CDCl_3$): δ 138.8, 132.7, 130.3, 115.5, 76.5, 68.9, 41.9, 41.4, 32.2, 31.4, 26.1, 22.5, 18.3, 14.2, -4.30. HRMS (EI) calcd for $C_{19}H_{36}O_2Si$ $[M]^+$ 324.2485, found 324.2422. IR (film): 2955, 2929, 2858, 1256, 1126, 1075, 911, 837, 775 cm^{-1}.

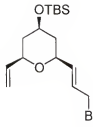


Figure 4-11. *cis*-4-*tert*-Butyldimethylsilyloxy-*cis*-[2-*E*-(3-bromo-propenyl)-6-ethenyl] tetrahydropyran (**329d**)

Oxabicyclic ether **327** (0.25g, 1.04mmol) and allyl bromide (0.45 mL, 5.2 mmol) were dissolved in chloroform (3 mL). A solution of **132** (8.9 mg, 0.01 mmol) in chloroform (0.5 mL) was added and the resulting solution allowed to stir under argon at room temperature. The reaction was monitored by NMR. Evaporation under reduced pressure and purification of the residue by silica gel chromatography using gradient elution (10:0 to 9.5:0.5, hexane:ethyl acetate) gave **329d** as a pale yellow oil (0.24g, 62%); R_f=0.37 (9.5:0.5, hexane:ethyl acetate). ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.98-5.77 (3H, m), 5.28 (1H, d, J=17.3 Hz), 5.14 (1H, d, J=10.5 Hz), 3.96 (2H, d, J=7.1 Hz), 3.89-3.81 (3H, m), 1.91-1.85 (2H, m), 1.40-1.27 (2H, m), 0.89 (9H, s), 0.081 (6H, s). ^{13}C NMR (300 MHz, $CDCl_3$): δ 138.4, 135.3, 127.1, 115.6, 76.6, 75.0, 68.6, 41.3, 41.2, 32.5, 26.0, 18.3, -4.3. HRMS (LSIMS) calcd for $C_{16}H_{28}O_2BrSi$ $[M-H]^+$ 359.1042, found 329.1020. IR (film): 2952, 2857, 1254, 1205, 1132, 1081, 964, 837, 776 cm^{-1}.

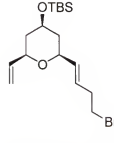


Figure 4-12. *cis*-4-*tert*-Butyldimethylsilyloxy-*cis*-[2-*E*-(4-bromo-but-1-enyl)-6-ethenyl] tetrahydropyran (**329e**)

Oxabicyclic ether **327** (0.25g, 1.04mmol) and 4-bromo-1-butene (0.53 mL, 5.2 mmol) were dissolved in chloroform (3 mL). A solution of **132** (8.9 mg, 0.01 mmol) in chloroform (0.5 mL) was added and the resulting solution allowed to stir under argon at room temperature. The reaction was monitored by NMR. Evaporation under reduced pressure and purification of the residue by silica gel chromatography using gradient elution (10:0 to 9.5:0.5, hexane:ethyl acetate) gave **329e** as a pale yellow oil (0.22g, 56%); R_f=0.35 (9.5:0.5, hexane:ethyl acetate). ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.88 (1H, ddd, J=17.3 Hz, 10.3 Hz, 5.9 Hz), 5.74-5.59 (2H, m), 5.27 (1H, d, J=17.3 Hz), 5.13 (1H, d, J=10.3 Hz), 3.90- 3.81 (3H, m), 3.40 (2H, t, J=7.1 Hz), 2.61 (2H, m), 1.90-1.83 (2H, m), 1.40-1.26 (2H, m), 0.89 (9H, s), 0.08 (6H, s). ^{13}C NMR (300 MHz, $CDCl_3$): δ 138.5, 133.5, 128.3, 115.6, 76.6, 75.9, 68.7, 41.6, 41.3, 35.9, 32.2, 26.0, 18.3, -4.3. HRMS (EI) calcd for $C_{16}H_{28}O_2BrSi$ $[M\text{-}CH_3]^+$ 359.1042, found 359.1090. IR (film): 2954, 2929, 2857, 1256, 1078, 837, 777 cm^{-1}.

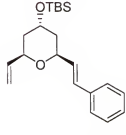


Figure 4-13. *trans-4-tert*-Butyldimethylsilyloxy-*cis*-[2-(*E*-2-phenylethenyl)-6-ethenyl] tetrahydropyran **(330a)**

Oxabicyclic ether **328** (0.05g, 0.21 mmol) and styrene (0.12 mL, 1.0 mmol) were dissolved in chloroform (0.47 mL). A solution of **132** (1.74 mg, 0.002 mmol) in chloroform (0.1 mL) was added and the resulting solution allowed to stir under argon at

room temperature. The reaction was monitored by NMR. Evaporation under reduced pressure and purification of the residue by silica gel chromatography using gradient elution (10:0 to 9.5:0.5, hexane:ethyl acetate) gave **330a** as a colorless oil (47.4 mg, 67%); R_f=0.47 (9.5:0.5, hexane:ethyl acetate). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.30-7.09 (5H, m), 6.54 (1H, d, J=15.9 Hz), 6.15 (1H, dd, J=15.9 Hz, 5.9 Hz), 5.82 (1H, ddd, J=16.9 Hz, 10.5 Hz, 5.4 Hz), 5.19 (1H, d, J=16.9 Hz), 5.04 (1H, d, J=10.5 Hz), 4.50-4.45 (1H, m), 4.38-4.32 (1H, m), 4.18 (1H, m), 1.63-1.46 (4H, m), 0.85 (9H, s), 0.00 (6H, s). ^{13}C NMR (300 MHz, $CDCl_3$): δ 139.5, 137.3, 130.9, 130.1, 128.7, 127.6, 126.6, 115.1, 72.6, 72.4, 65.0, 39.5, 39.1, 26.0, 18.3, -4.6. HRMS (CI) calcd for $C_{21}H_{33}O_2Si$ $[M+H]^+$ 345.2250, found 345.2225. IR (film): 2952, 2856, 1254, 1092, 1053, 965, 914, 834, 772, 693 cm^{-1}.

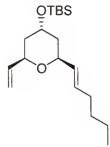


Figure 4-15. *trans*-4-*tert*-Butyldimethylsilyloxy-*cis*-[2-(*E*-hex-1-enyl)-6-ethenyl] tetrahydropyran (**330b**)

Oxabicyclic ether **328**(0.05g, 0.21mmol) and 1-hexene (0.13 mL, 1.0 mmol) were dissolved in chloroform (0.6 mL). A solution of **131** (1.8 mg, 0.002 mmol) in chloroform (0.1 mL) was added and the resulting solution allowed to stir under argon at room temperature. The reaction was monitored by NMR. Evaporation under reduced pressure and purification of the residue by silica gel chromatography using gradient elution (10:0 to 9.5:0.5, hexane:ethyl acetate) gave **330b** as a colorless oil (57 mg, 75%); R_f=0.41

(9.5:0.5, hexane:ethyl acetate). ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.88 (1H, ddd, J=17.3 Hz, 10.4 Hz, 5.7 Hz), 5.69 (1H, dt, J=15.5 Hz, 6.7 Hz), 5.49 (1H, dd, J=15.5 Hz, 6.3 Hz), 5.25 (1H, d, J=17.3 Hz), 5.09 (1H, d, J=10.4 Hz) 4.39-4.304 (2H, m), 4.23-4.21 (1H, m), 2.05-2.01 (2H, m), 1.62-1.48 (4H, m), 1.40-1.27 (4H, m), 0.94-0.86 (12H, m), 0.06-0.08 (6H, s). ^{13}C NMR (300 MHz, $CDCl_3$): δ 139.7, 132.1, 131.1, 114.9, 72.5, 72.4, 65.1, 39.7, 39.1, 32.3, 31.4, 25.0, 22.5, 18.3, 14.2, -4.6. HRMS (CI) calcd for $C_{19}H_{37}O_2Si$ $[M+H]^+$ 325.2563, found 325.2574. IR (film): 2955, 2928, 2857, 1254, 1088, 1055, 1033, 914, 834, 773 cm^{-1}.

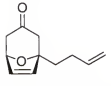


Figure 4-16. 1-But-3-enyl-8-oxabicyclo[3.2.1]oct-6-en-3-one (**344a**)

Under an atmosphere of argon, furan (1.60 mL, 0.022 mol) was added dropwise to a stirred solution of *n*-butyl lithium (8.16 mL, 0.022 mol) in dry THF (14.69 mL) cooled to -15°C in a dry ice/ethylene glycol bath. The solution was allowed to warm to room temperature and to stir for 20 minutes. 4-bromo-1-butene (2.24 mL, 0.022 mol) was then added dropwise and the reaction allowed to stir at room temperature. After two hours, the reaction was quenched by pouring the solution onto ice. The aqueous layer was then extracted four times with 25 mL portions of diethyl ether. The organic layers were combined and dried on Na_2SO_4. The mixture was then filtered and the solvent removed *in vacuo*. The crude yellow oil (2.66 g) was added to a dry 200 mL round bottom flask without purification and cooled to 0° C. Via two separate 100 mL addition funnels, solutions of sodium trifluoroethoxide (2M, 65.0 mL) and trichloroacetone (6.91 mL, 0.07 mol) in trifluoroethanol (58.1 mL) were added simultaneously and dropwise. Upon

completion of addition, the solution was allowed to warm to room temperature. The reaction was monitored by TLC, using $KMnO_4$ as a stain. After 1 hour, an equal volume of water (40 mL) and dichloromethane (40 mL) was added and the aqueous layer extracted three times with 40 mL portions of dichloromethane. The organic layers were combined, dried on $MgSO_4$, filtered and the solvent removed *in vacuo*. The crude yellow/brown solid was added to a 100 mL round bottom flask without purification. Zinc/copper couple (7.33 g) and a solution of methanol saturated with ammonium chloride (40 mL) were added and the flask placed in a sonicator at 60° C for 6 hours. The mixture was then filtered through celite, washing with ethyl acetate, to remove the zinc/copper couple. The filtrate was then evaporated and the residue re-dissolved in a saturated solution of EDTA (15 mL) and dichloromethane (30 mL). The aqueous layer was extracted four times with dichloromethane (40 mL). The organic layers were combined and dried on $MgSO_4$, filtered, and the solvent removed in vacuo. Purification of the residue by silica gel chromatography (90:1 silica gel: residue; 9:1 hexane: ethyl acetate) gave **344a** as a pale, yellow oil (1.24 g, 31.7% over 3 steps). R_f=0.35 (3:1 hexane: ethyl acetate). ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.19 (1H, dd, J=5.9 Hz, 1.5 Hz), 6.05 (1H, d, J=5.9 Hz), 5.79-5.93 (1H, m), 4.97-5.09 (3H, m), 2.70 (1H, dd, J=16.4 Hz, 5.0 Hz), 2.54 (1H, d, J=16.1 Hz), 2.38 (1H, d, J=16.1 Hz), 2.30 (1H, d, J=16.4 Hz), 2.07-2.26 (2H, m), 1.83-1.89 (2H, m). ^{13}C NMR (300 MHz, $CDCl_3$): δ 206.6, 138.4, 135.5, 133.9, 115.3, 86.5, 77.9, 51.7, 45.9, 35.9, 28.6. HRMS (EI) calcd for $C_{11}H_{14}O_2$ $[M]^+$ 178.0994, found 178.1007. IR (film): 2953.4, 1717, 1641, 1344, 1209, 1019, 918, 854, 736 cm^{-1}.

Figure 4-17. 7-vinyl-6-oxa-spiro[4.5]dec-1-ene-9-one (**345a**)

A solution of oxabicyclic ketone **344a** (62.7mg, 0.337 mmol) in dichloromethane (32.7 mL) was prepared. A solution of **132** (14.9 mg, 0.017 mmol) in dichloromethane (1 mL) was added and the resulting solution allowed to stir under argon at room temperature. The reaction was monitored by TLC, using p-anisaldehyde as a stain. After 72 hours, evaporation under reduced pressure and purification of the residue by silica gel chromatography (100:1 silica gel: residue; 9.5:0.5 hexane: ether) gave **345a** as a pale, yellow oil (35 mg, 56%). Unreacted starting material **344a** (10 mg, 16%) was recovered. R*f*=0.45 (3:1 hexane: ethyl acetate). ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.87-5.98 (2H, m), 5.72-5.75 (1H, m), 5.30 (1H, d, J=17.2 Hz), 5.20 (1H, d, J=10.2 Hz), 4.30 (1H, dd, J= 13.7 Hz, 6.1 Hz), 2.62 (1H, d, J=13.4 Hz), 2.30-2.58 (4H, m), 2.26 (1H, d, 13.4 Hz), 1.89-1.94 (2H, m). ^{13}C NMR (300 MHz, $CDCl_3$): δ 206.8, 137.7, 135.4, 134.0, 116.6, 90.6, 73.4, 50.7, 47.6, 33.4, 31.5. HRMS (EI) calcd for $C_{11}H_{14}O_2$ $[M]^+$ 178.0994, found 178.1005. IR (film): 3060, 2962, 2932, 2855, 1721, 1360, 1285, 1262, 1076, 924, 737 cm^{-1}.

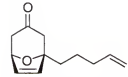


Figure 4-18. 1-Pent-4-enyl-8-oxabicyclo[3.2.1]oct-6-en-3-one (**344b**)

Under an atmosphere of argon, furan (1.07 mL, 0.015 mol) was added dropwise to a stirred solution of *n*-butyl lithium (5.44 mL, 0.015 mol) in dry THF (9.79 mL) cooled to -15°C in a dry ice/ethylene glycol bath. The solution was allowed to warm to room temperature and to stir for 20 minutes. 5-bromo-1-pentene (1.74 mL, 0.015 mol) was then added dropwise and the reaction allowed to stir at room temperature. After two hours, the reaction was quenched by pouring the solution onto ice. The aqueous layer was then extracted four times with 25 mL portions of diethyl ether. The organic layers were combined and dried on Na_2SO_4. The mixture was then filtered and the solvent removed *in vacuo*. The crude, yellow oil (1.65 g) was added to a dry 200 mL round bottom flask without purification and cooled to 0° C. Via two separate 50 mL addition funnels, solutions of sodium trifluoroethoxide (2M, 36.4 mL) and trichloroacetone (3.85 mL, 0.04 mol) in trifluoroethanol (32.4 mL) were added simultaneously and dropwise. Upon completion of addition, the solution was allowed to warm to room temperature. The reaction was monitored by TLC, using $KMnO_4$ as a stain. After 1 hour, an equal volume of water (40 mL) and dichloromethane (40 mL) was added and the aqueous layer extracted three times with 40 mL portions of dichloromethane. The organic layers were combined, dried on $MgSO_4$, filtered and the solvent removed *in vacuo*. The crude yellow/brown solid was added to a 100 mL round bottom flask without purification. Zinc/copper couple (4.0 g) and a solution of methanol saturated with ammonium chloride (40 mL) were added and the flask placed in a sonicator at 60° C for 6 hours. The mixture was then filtered through celite, washing with ethyl acetate, to remove the zinc/copper couple. The filtrate was then evaporated and the residue re-dissolved in a saturated solution of EDTA (15 mL) and dichloromethane (30 mL). The aqueous layer was

extracted four times with dichloromethane (40 mL). The organic layers were combined and dried on $MgSO_4$, filtered, and the solvent removed in vacuo. Purification of the residue by silica gel chromatography (90:1 silica gel: residue; 9:1 hexane: ethyl acetate) gave **345b** as a pale, yellow oil (1.65 g, 71.4 % over 3 steps). R*f*=0.40 (3:1 hexane: ethyl acetate). ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.18 (1H, dd, J= 6.0 Hz, 1.5 Hz), 6.04 (1H, d, J=6.0 Hz), 5.74-5.87 (1H, m), 4.96-5.06 (3H, m), 2.69 (1H, dd, J=16.2 Hz, 5.0 Hz), 2.53 (1H, d, J= 16.1 Hz), 2.36 (1H, d, J= 16.1 Hz), 2.29 (1H, d, J=16.2 Hz), 2.11 (2H, dd, J=14.3 Hz, 7.2 Hz), 1.74-1.80 (2H, m), 1.42-1.66 (2H, m). ^{13}C NMR (300 MHz, $CDCl_3$): δ 206.5, 138.5, 135.4, 133.6, 115.2, 86.5, 77.6, 51.5, 45.7, 35.9, 34.0, 23.3. HRMS (EI) calcd for $C_{12}H_{16}O_2$ $[M]^+$ 192.1150, found 192.1149. IR (film): 2932, 2855, 1721, 1285, 1076, 924, 737 cm^{-1}.

Figure 4-19. 2-vinyl-1-oxaspiro[5.5]undec-7-en-4-one (**345b**)

A solution of oxabicyclic ketone **344b** (82.4mg, 0.429 mmol) in dichloromethane (41.9 mL) was prepared. A solution of **132** (9.11 mg, 0.011 mmol) in dichloromethane (1 mL) was added and the resulting solution allowed to stir under argon at room temperature. The reaction was monitored by TLC, using p-anisaldehyde as a stain. After 3 hours, evaporation under reduced pressure and purification of the residue by silica gel chromatography (100:1 silica gel: residue; 9.5:0.5 hexane: ether) gave **345b** as a pale, yellow oil (67.4 mg, 82%). Unreacted starting material **344b** (7.9 mg, 10%) was

recovered. R*f*=0.68 (3:2 hexane: ethyl acetate). ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.85-5.98 (2H, m), 5.61 (1H, dt, J=10.2 Hz, 2.1 Hz), 5.29 (1H, dt. J=17.1 Hz, 1.1 Hz), 5.19 (1H, dt, J=10.2 Hz, 1.1 Hz), 4.40 (1H, ddt, J= 13.8 Hz, 6.6 Hz, 1.1 Hz), 2.37-2.46 (4H, m), 1.93-2.14 (2H, m), 1.67-1.85 (3H, m), 1.15 -1.61 (1H, m). ^{13}C NMR (300 MHz, $CDCl_3$): δ 207.3, 138.0, 131.7, 130.9, 116.5, 75.6, 71.6, 51.4, 47.3, 31.0, 25.0, 19.1. HRMS (EI) calcd for $C_{12}H_{16}O_2$ $[M]^+$ 192.1150, found 192.1150. IR (film): 2935, 2867, 1721, 1307, 1056, 986, 927, 738 cm^{-1}.

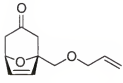


Figure 4-20. 1-Allyloxymethyl-8-oxabicyclo[3.2.1]oct-6-en-3-one (**344c**)

At 0° C, via two separate 50 mL addition funnels, solutions of sodium trifluoroethoxide (2M, 32.6 mL) and trichloroacetone (3.45 mL, 0.03 mol) in trifluoroethanol (29.0 mL) were added simultaneously and dropwise to a 100 mL round bottom flask containing 2-allyloxymethyl furan (1.5g, 0.011 mol). Upon completion of addition, the solution was allowed to warm to room temperature. The reaction was monitored by TLC, using $KMnO_4$ as a stain. After 1 hour, an equal volume of water (20 mL) and dichloromethane (20 mL) was added and the aqueous layer extracted three times with 40 mL portions of dichloromethane. The organic layers were combined, dried on $MgSO_4$, filtered and the solvent removed *in vacuo*. The crude yellow/brown solid was added to a 100 mL round bottom flask without purification. Zinc/copper couple (4.0 g) and a solution of methanol saturated with ammonium chloride (20 mL) were added and the flask placed in a sonicator at 60° C for 6 hours. The mixture was then filtered through celite, washing with ethyl acetate, to remove the zinc/copper couple. The filtrate

was then evaporated and the residue redissolved in a saturated solution of EDTA (15 mL) and dichloromethane (30 mL). The aqueous layer was extracted four times with dichloromethane (40 mL). The organic layers were combined and dried on $MgSO_4$, filtered, and the solvent removed *in vacuo*. Purification of the residue by silica gel chromatography (90:1 silica gel: residue; 9:1 hexane: ethyl acetate) gave **344c** as a pale, yellow oil (1.28g; 60%). R*f*=0.25 (3:1 hexane: ethyl acetate). ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.26 (1H, dd, J=5.8 Hz, 1.5 Hz), 6.11 (1H, d, J= 5.8 Hz), 5.85-5.98 (1H, m), 5.29 (1H, d, J=17.4 Hz), 5.22 (1H, d, J=10.5 Hz), 5.11 (1H, d, J=5.0 Hz), 4.09 (2H, d, J=5.9 Hz), 3.66 (2H, s), 2.74 (1H, d, J=16.5 Hz), 2.73 (1H, d, J=16.5 Hz), 2.37 (1H, d, J=15.5 Hz), 2.31 (1H, d, J=15.5 Hz). ^{13}C NMR (300 MHz, $CDCl_3$): δ 205.9, 134.4, 134.3, 133.7, 117.8, 86.1, 78.0, 72.8, 72.0, 48.1, 45.5. HRMS (EI) calcd, for $C_{11}H_{14}O_3$ $[M]^+$ 194.0943, found 194.0924. IR (film): 3082, 2906, 2956, 1717, 1650, 1406, 1328, 1288, 1163, 1126, 1099, 1021, 917, 854, 733 cm^{-1}.

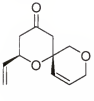


Figure 4-21. 2-vinyl-1,8-dioxaspiro[5.5]undec-10-en-4-one (**345c**)

A solution of oxabicyclic ketone **344c** (66.0mg, 0.34 mmol) in dichloromethane (33.0 mL) was prepared. A solution of **132** (7.20 mg, 0.009 mmol) in dichloromethane (1 mL) was added and the resulting solution allowed to stir under argon at room temperature. The reaction was monitored by TLC, using p-anisaldehyde as a stain. After 3 hours, evaporation under reduced pressure and purification of the residue by silica gel chromatography (100:1 silica gel: residue; 9:1 hexane: ethyl acetate) gave **345c** as a pale, yellow oil (53.0 mg, 80%). R*f*=0.25 (3:1 hexane: ethyl acetate). ^{1}H NMR (300 MHz,

$CDCl_3$): δ 5.76-5.96 (3H, m), 5.30 (1H, d, J=17.2 Hz), 5.21 (1H, d, J=10.5 Hz), 4.30-4.38 (1H, m), 4.05-4.18 (2H, m), 3.66-3.79 (2H, m), 2.64 (1H, d, J=14.6 Hz), 2.42-2.44 (3H, m). ^{13}C NMR (300 MHz, $CDCl_3$): δ 206.10, 137.4, 129.6, 128.6, 116.9, 72.6, 69.4, 65.4, 48.3, 47.1, 10.3. HRMS (EI) calcd for $C_{11}H_{14}O_3$ $[M]^+$ 194.0943, found 194.0926. IR (film): 2855, 1718, 1316, 1257, 1164, 1094, 1045, 1022, 972, 719 cm^{-1}.

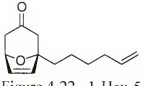


Figure 4-22. 1-Hex-5-enyl-8-oxabicyclo[3.2.1]oct-6-ene-3-one (**344d**)

Under an atmosphere of argon, furan (2.23 mL, 0.031 mol) was added dropwise to a stirred solution of *n*-butyl lithium (11.36 mL, 0.031 mol) in dry THF (30.7 mL) cooled to -15°C in a dry ice/ethylene glycol bath. The solution was allowed to warm to room temperature and to stir for 20 minutes. 6-bromo-1-hexene (4.11 mL, 0.031 mol) was then added dropwise and the reaction allowed to stir at room temperature. After two hours, the reaction was quenched by pouring the solution onto ice. The aqueous layer was then extracted four times with 30 mL portions of diethyl ether. The organic layers were combined and dried on Na_2SO_4. The mixture was then filtered and the solvent removed *in vacuo*. The crude yellow oil (5.30 g) was added to a dry 250 mL round bottom flask without purification and cooled to 0° C. Via two separate 150 mL addition funnels, solutions of sodium trifluoroethoxide (2M, 106 mL) and trichloroacetone (11.21 mL, 0.11 mol) in trifluoroethanol (95 mL) were added simultaneously and dropwise. Upon completion of addition, the solution was allowed to warm to room temperature. The reaction was monitored by TLC, using $KMnO_4$ as a stain. After 1 hour, an equal volume of water (50 mL) and dichloromethane (50 mL) was added and the aqueous layer

extracted three times with 50 mL portions of dichloromethane. The organic layers were combined, dried on $MgSO_4$, filtered and the solvent removed *in vacuo*. The crude yellow/brown solid was added to a 100 mL round bottom flask without purification. Zinc/copper couple (21.9 g) and a solution of methanol saturated with ammonium chloride (50 mL) were added and the flask placed in a sonicator at 60° C for 4 hours. The mixture was then filtered through celite, washing with ethyl acetate, to remove the zinc/copper couple. The filtrate was then evaporated and the residue re-dissolved in a saturated solution of EDTA (20 mL) and dichloromethane (60 mL). The aqueous layer was extracted four times with dichloromethane (60 mL). The organic layers were combined and dried on $MgSO_4$, filtered, and the solvent removed *in vacuo*. Purification of the residue by silica gel chromatography using gradient elution (100:1 silica gel: residue; 97:3; 95:5; 96:4; 92:8 hexane: ethyl acetate) gave **344d** as a pale, yellow oil (3.81 g, 60.3 % over 3 steps). R*f*=0.37 (3:1 hexane: ethyl acetate). ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.18 (1H dd, J=5.9 Hz, 1.7 Hz), 6.03 (1H, d, J=5.9 Hz), 5.73-5.87 (1H, m), 4.93-5.05 (3H, m), 2.69 (1H, dd, J= 16.2 Hz, 5.0 Hz), 2.52 (1H, d, J=16.2 Hz), 2.35 (1H, d, J=16.3 Hz), 2.22 (1H, d, J=16.3 Hz), 2.07 (2H, dd, J= 14.0 Hz, 6.7 Hz), 1.70-1.81 (2H, m), 1.31-1.52 (4H, m). ^{13}C NMR (300 MHz, $CDCl_3$): δ 206.5, 138.8, 135.4, 133.5, 114.8, 86.5, 77.6, 51.4, 45.7, 36.4, 33.8, 29.3, 23.5. HRMS (EI) calcd for $C_{13}H_{18}O_2$ $[M]^+$ 206.1307, found 206.1299. IR (film): 3076, 2935, 2861, 1717, 1641, 1344, 1204, 1023, 917, 854, 731 cm^{-1}.

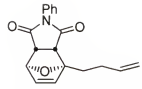


Figure 4-23. 1-But-3-enyl-4-phenyl-10-oxa-4-aza-tricyclo[5.2.1.$0^{2,6}$]dec-8-ene-3,5-dione (**357a**)

2-but-3-enyl-furan (0.5g, 4.1 mmol) and n-phenyl maleimide (1.06g, 6.15 mmol) were dissolved in a minimum volume of dichloromethane and heated in a sealed tube to 100° C for 24 hours. Evaporation under reduced pressure and purification by silica gel chromatography using gradient elution (92:8 hexane:ether; 85:15 hexane:ethyl acetate; 3:2 hexane:ethyl acetate) gave **357a**, the major isomer, as a solid (0.44g, 37%). R*f*=0.34 in (3:2 hexane: ethyl acetate). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.26-7.48 (5H, m), 6.52 (1H, d, J=5.9 Hz), 6.42 (1H, d, J=5.9 Hz), 5.83-5.96 (1H, m), 5.30 (1H, s), 5.08 (1H, d, J=10.0 Hz), 5.00 (1H, d, J= 17.1 Hz), 3.08 (1H, d, J=6.4 Hz), 2.89 (1H, d, J=6.4 Hz), 2.08-2.43 (4H, m). ^{13}C NMR (300 MHz, $CDCl_3$): δ175.4, 174.0, 138.9, 137.8, 137.2, 131.8, 129.2, 128.8, 126.6, 115.2, 92.0, 81.0, 50.6, 49.2, 29.6, 29.1. HRMS (EI) calcd for $C_{18}H_{17}NO_3$ $[M]^+$ 295.1208, found 295.1190. IR (film): 3470, 3077, 2978, 2950, 2928, 1777, 1715, 1501, 1385, 1192, 918, 888, 721 cm^{-1}.

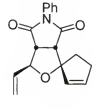


Figure 4-24. 7-phenyl-4-vinyl-spiro[7-aza-3-oxabicyclo[3.3.0]octane-2,1'-cyclopent-2'-ene-6,8-dione (**358a**)

A solution of oxa-azatricyclic dione **357a** (60.0mg, 0.20 mmol) in dichloromethane (19.3 mL) was prepared. A solution of **132** (8.63 mg, 0.01 mmol) in dichloromethane (1 mL) was added and the resulting solution allowed to stir under argon at room temperature. The reaction was monitored by TLC, using p-anisaldehyde as a stain. After 12 hours, evaporation under reduced pressure and purification of the residue by silica gel chromatography (100:1 silica gel: residue; 9:1 hexane: ethyl acetate) gave **358a** as a solid (50.6 mg, 84%). R*f*=0.25 (3:1 hexane: ethyl acetate). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.26-7.51 (5H, m), 5.98-6.12 (2H, m), 5.80-5.82 (1H, m), 5.46 (1H, d, J=17.2 Hz), 5.30 (1H, d, J=10.5 Hz), 4.72-4.74 (1H, m), 3.48-3.56 (2H, m), 2.27-2.60 (3H, m), 1.93-2.04 (1H, m). ^{13}C NMR (300 MHz, $CDCl_3$): δ 175.8, 174.8, 137.2, 136.7, 133.9, 131.7, 129.4, 128.9, 126.5, 117.8, 96.6, 80.4, 53.9, 53.0, 32.7, 31.7. HRMS (EI) calcd for $C_{18}H_{17}NO_3$ $[M]^+$ 295.1208, found 295.1206. IR (film): 3064, 2928, 1855, 1715, 1381, 1180, 1057, 730, 691 cm^{-1}.

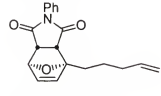


Figure 4-25. 1-Pent-4-enyl-4-phenyl-10-oxa-4-aza-tricyclo[5.2.1.$0^{2,6}$]dec-8-ene-3,5-dione (**357b**)

2-pent-4-enyl-furan (0.10g, 0.7 mmol) and n-phenyl maleimide (0.19g, 1.10 mmol) were dissolved in a minimum volume of dichloromethane and heated in a sealed tube to 100° C for 24 hours. Evaporation under reduced pressure and purification by silica gel chromatography using gradient elution (92:8 hexane:ether; 85:15 hexane:ethyl acetate; 3:2 hexane:ethyl acetate) gave **357b**, the major isomer, as a solid (0.23g, 99%). R*f*=0.21 in (3:1 hexane: ethyl acetate). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.26-7.49 (5H, m), 6.55

(1H, d, J=5.9 Hz), 6.43 (1H, d, J=5.9 Hz), 5.76-5.90 (1H. m), 5.29-5.33 (1H, m), 4.96-5.07 (2H, m), 3.11 (1H, d, J=6.4 Hz), 2.01 (1H, d, J=6.4 Hz), 1.98-2.20 (4H, m), 1.57-1.78 (2H, m). ^{13}C NMR (300 MHz, $CDCl_3$): δ 175.6, 174.2, 139.2, 138.4, 137.3, 131.9, 129.3, 128.9, 126.8, 115.2, 92.4, 81.1, 50.7, 49.2, 34.1, 29.4, 24.8. HRMS (EI) calcd for $C_{19}H_{19}NO_3$ $[M]^+$ 309.1365, found 309.1364. IR (film): 2926, 1777, 1713, 1501, 1383, 1193, 897, 718, 701 cm^{-1}.

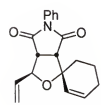


Figure 4-26. 7-phenyl-4-vinyl-spiro[7-aza-3-oxabicyclo[3.3.0]octane-2,1'-cyclohex-2'-ene-6,8-dione (**358b**)

A solution of oxa-azatricyclic dione **357b** (45.0mg, 0.146 mmol) in dichloromethane (11.9 mL) was prepared. A solution of **132** (6.2 mg, 0.007 mmol) in dichloromethane (1 mL) was added and the resulting solution allowed to stir under argon at room temperature. The reaction was monitored by TLC, using p-anisaldehyde as a stain. After 1 hour, evaporation under reduced pressure and purification of the residue by silica gel chromatography (200:1 silica gel: residue; 3:2 hexane: ethyl acetate) gave **358b** as a solid (35.0 mg, 78%). R*f*=0.33 (3:1 hexane: ethyl acetate). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.27-7.51 (5H, m), 5.98-6.10 (2H, m), 5.69 (1H, d, J=9.9 Hz), 5.45 (1H, d, J=17.2 Hz), 5.29 (1H, d, J=10.5 Hz), 4.79-4.82 (1H, m), 3.55 (1H, dd, J=9.5 Hz, 5.0 Hz), 3.45 (1H, d, J= 9.5 Hz), 1.92-2.18 (2H, m), 1.78-1.90 (4H, m). ^{13}C NMR (300 MHz, $CDCl_3$): δ 175.8, 174.3, 137.6, 133.2, 131.7, 130.2, 129.4, 128.9, 126.5, 117.7, 82.6,

79.9, 50.1, 53.6, 29.6, 24.9, 19.1. HRMS (EI) calcd for $C_{19}H_{19}NO_3$ $[M]^+$ 309.1365, found 309.1362. IR (film): 2935, 1779, 1715, 1598, 1498, 1381, 1186, 919, 739, 691 cm^{-1}.

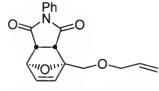


Figure 4-27. 1-Allyloxymethyl-4-phenyl-10-oxa-4-aza-tricyclo[5.2.1.$0^{2,6}$]dec-8-ene-3,5-dione (**357c**)

2-allyloxymethylfuran (0.4g, 2.9 mmol) and *n*-phenyl maleimide (0.75g, 4.3 mmol) were dissolved in a minimum volume of dichloromethane and heated in a sealed tube to 100° C for 24 hours. Evaporation under reduced pressure and purification by silica gel chromatography (100:1 silica gel:compound; 3:2 hexane:ethyl acetate) gave **357c**, the major isomer, as a solid (0.53g, 60%). R*f*=0.25 (3:2 hexane:ethyl acetate). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.37-7.50 (3H, m), 7.26-7.29 (2H, m), 6.60 (2H, s), 5.87-6.01 (1H, m), 5.39 (1H, d, J= 1.2 Hz), 5.30 (1H, dd, J= 17.1 Hz, 1.7 Hz), 5.21 (1 H, dd, J=10.2 Hz, 1.7 Hz), 4.23 (1H, d, J= 11.4 Hz), 4.06-4.19 (2H, m), 3.93 (1H, d, J=11.4 Hz), 3.14 (1H, d, J= 6.5 Hz), 3.03 (1H, d, J=6.5 Hz). ^{13}C NMR (300 MHz, $CDCl_3$): δ 175.3, 174.0, 138.4, 137.1, 134.5, 131.9, 129.4, 129.0, 126.8, 117.9, 91.1, 81.7, 73.0, 67.6, 50.2, 48.6. HRMS (EI) calcd for $C_{18}H_{17}NO_4$ $[M]^+$ 311.1158, found 312.1158. IR (film): 2869, 1777, 1713, 1499, 1384, 1193, 1109, 938, 720 cm^{-1}.

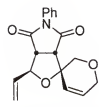


Figure 4-28. 7-phenyl-4-vinyl-spiro[7-aza-3-oxabicyclo[3.3.0]octane-2,3'-ox-4'-ene-6,8-dione (**358c**)

A solution of oxa-azatricyclic dione **357c** (62.5mg, 0.193mmol) in dichloromethane (18.3 mL) was prepared. A solution of **132** (8.18mg, 0.010 mmol) in dichloromethane (1 mL) was added and the resulting solution allowed to stir under argon at room temperature. The reaction was monitored by TLC, using p-anisaldehyde as a stain. After 24 hours, evaporation under reduced pressure and purification of the residue by silica gel chromatography (100:1 silica gel: residue; 3:1 hexane: ethyl acetate) gave **358c** as a solid (59.2 mg, 95%). R_f=0.18 (3:2 hexane:ethyl acetate). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.38-7.51 (3H, m), 7.26-7.30 (2H, m), 5.99-6.11 (2H, m), 5.88 (1H, dd, J=10.2 Hz, 1.0 Hz), 5.46 (1H, ddd, J=17.1 Hz, 1.4 Hz, 1.0 Hz), 5.30 (1H, ddd, J=10.5 Hz, 1.4 Hz, 1.0 Hz), 4.90 (1H, ddt, J=5.5 Hz, 4.8 Hz, 1.4 Hz), 4.10-4.27 (2H, m), 4.01 (1H, d, J=11.9 Hz), 3.85 (1H, dd, J=11.9 Hz, 1.0 Hz), 3.60 (1H, dd, J=9.0 Hz, 4.8 Hz), 3.46 (1H, d, J= 9.03 Hz). ^{13}C NMR (300 MHz, $CDCl_3$): δ 175.5, 173.1, 137.6, 131.6, 130.5, 129.5, 129.1, 128.2, 126.5, 117.7, 80.9, 79.8, 68.4, 65.2, 53.8, 53.0. HRMS (EI) calcd for $C_{18}H_{17}NO_4$ $[M]^+$ 311.1158, found 311.1144. IR (film): 2954, 2829, 1779, 1714, 1498, 1382, 1190, 1096, 738, 691 cm^{-1}.

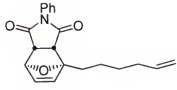


Figure 4-29. 1-Hex-5-enyl-4-phenyl-10-oxa-4-aza-tricyclo[5.2.1.$0^{2,6}$]dec-8-ene-3,5-dione (**357d**)

2-hex-5-enyl furan (0.3g, 2 mmol) and n-phenyl maleimide (0.52g, 3 mmol) were dissolved in a minimum volume of dichloromethane and heated in a sealed tube to 100° C for 24 hours. Evaporation under reduced pressure and purification by silica gel chromatography using gradient elution (9:1 hexane:ether; 8:2 hexane:ether; 65:35 hexane:ether) gave **357d**, the major isomer, as a white solid (0.40g, 63%). R*f*=0.40 (3:2 hexane:ethyl acetate). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.36-7.50 (3H, m), 7.26-7.29 (2H, m), 6.55 (1H, d, J=5.7 Hz), 6.43 (1H, d, J=5.70 Hz), 5.74-5.88 (1H, m), 5.32 (1H, d, J=1.4 Hz), 4.92-5.05 (2H, m), 3.11 (1H, d, J=6.7 Hz), 2.91 (1H, d, J=6.7 Hz), 1.97-2.13 (4H, m), 1.48-1.68 (4H, m). ^{13}C NMR (300 MHz, $CDCl_3$): δ 175.5, 174.2, 139.3, 138.9, 137.3, 131.9, 129.3, 128.9, 126.8, 114.8, 92.4, 81.1, 50.7, 49.2, 33.7, 29.7, 29.3, 25.0. HRMS (EI) calcd for $C_{20}H_{21}NO_3$ $[M]^+$ 323.1521, found 323.1537. IR (film): 2930, 1777, 1714, 1501, 1384, 1193, 942, 718 cm^{-1}.

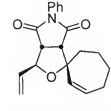


Figure 4-30. 7-phenyl-4-vinyl-spiro[7-aza-3-oxabicyclo[3.3.0]octane-2,1'-cyclohept-2'-ene-6,8-dione (**358d**)

A solution of oxa-azatricyclic dione **358d** (60.0mg, 0.186 mmol) in dichloromethane (17.6 mL) was prepared. A solution of **132** (7.89 mg, 0.009 mmol) in dichloromethane (1 mL) was added and the resulting solution allowed to stir under argon at room temperature. The reaction was monitored by TLC, using p-anisaldehyde as a stain. After 24 hours, evaporation under reduced pressure and purification of the residue by silica gel chromatography (150:1 silica gel: residue; 3:2 hexane: ethyl acetate) gave **358d** as a white solid (32.1 mg, 54%). Unreacted starting material **357d** (11.4 mg, 19%) was recovered. R*f*=0.34 (3:1 hexane:ethyl acetate). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.26-7.51 (5H, m), 5.94-6.12 (2H, m), 5.70 (1H, dd, J=9.5 Hz, 1.2 Hz), 5.46 (1H, dt, J=17.1 Hz, 1.2 Hz), 5.29 (1H, dt, J=10.5 Hz, 1.2 Hz), 4.70 (1H, ddt, J=6.1 Hz, 5.4 Hz, 1.2 Hz), 3.45-3.55 (2H, m), 2.11-2.33 (2H, m), 1.53-2.0 (6H, m). ^{13}C NMR (300 MHz, $CDCl_3$): δ 175.8, 174.2, 137.4, 135.8, 135.2, 131.8, 129.4, 129.0, 126.5, 117.8, 87.3, 80.0, 58.5, 53.3, 31.0, 27.1, 26.7, 23.1. HRMS (EI) calcd for $C_{20}H_{21}NO_3$ $[M]^+$ 323.1521, found 323.1522. IR (film): 2929, 1715, 1500, 1380, 1181, 990, 691 cm^{-1}.

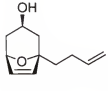


Figure 4-31. (3-*endo*)-1-But-3-enyl-8-oxabicyclo[3.2.1]oct-6-en-3-ol (**359**)

Under an atmosphere of argon, a solution of **344a** (0.25g, 1.4 mmol) in THF (1.4 mL) was cooled to -78°C in a dry ice/acetone bath. L-selectride (1M in THF, 1.69 mL) was added dropwise and the reaction held at -78°C for one hour then allowed to warm slowly to room temperature. After an additional hour, the reaction was cooled to 0°C and a solution of 20% NaOH (2mL) and 30% H_2O_2 (1 mL) was added dropwise. After one hour, the solution was neutralized with 2M H_2SO_4. The aqueous layer was saturated with

NaCl and extracted with ethyl acetate. The organic layers were combined, dried on $MgSO_4$, filtered and the solvent removed *in vacuo*. Purification by silica gel chromatography using gradient elution (100:1 silica gel:residue; 95:5 to 70:30 hexane:ethyl acetate) gave **359** as a colorless oil. R*f*=0.21 (3:2 hexane:ethyl acetate). ^1H NMR (300 MHz, $CDCl_3$): δ 6.40-6.42 (1H, m), 6.22-6.24 (1H, m), 5.77-5.91 (1H, m), 5.03 (1H, dd, J=17.2 Hz, 1.7 Hz), 4.95 (1H, dd, J=10.2 Hz, 1.7 Hz), 4.80 (1H, s), 3.99-4.23 (1H, m), 2.01-2.26 (5H, m), 1.67-1.81 (4H, m). ^{13}C NMR (300 MHz, $CDCl_3$): δ 138.7, 137.7, 136.3, 114.7, 85.5, 78.8, 65.9, 41.3, 36.5, 35.8, 28.1. HRMS (EI) calcd for $C_{11}H_{16}O_2$ $[M]^+$ 180.1150, found 180.1141. IR (film): 3432, 3076, 2939, 1641, 1348, 1073, 1031, 913, 871, 693 cm^{-1}.

Figure 4-32. (5S*, 7R*, 9R*)-7-Vinyl-6-oxa-spiro[4.5]dec-1-en-9-ol (**360**)

A solution of oxabicyclic alcohol **359** (30.0 mg, 0.167mmol) in dichloromethane (17.9 mL) was prepared. A solution of **132** (7.08 mg, 0.008 mmol) in dichloromethane (1 mL) was added and the resulting solution allowed to stir under argon at room temperature. The reaction was monitored by TLC, using p-anisaldehyde as a stain. After 30 minutes, evaporation under reduced pressure and purification of the residue by silica gel chromatography (100:1 silica gel: residue; 3:1 hexane: ethyl acetate) gave **360** as a colorless oil (23.3 mg, 83%). R*f*=0.28 (3:2 hexane:ethyl acetate). ^1H NMR (300 MHz, $CDCl_3$): δ 5.82-5.93 (2H, m), 5.62-5.65 (1H, m), 5.25 (1H, dt, J= 17.4 Hz, 1.4 Hz), 5.12 (1H, dt, J= 10.5 Hz, 1.4 Hz), 3.93-4.05 (2H, m), 2.46-2.58 (1H, m), 2.30-2.42 (1H, m),

1.82-2.06 (4H, m), 1.67 (1H, s), 1.46 (1H, m), 1.23-1.35 (1H, m). ^{13}C NMR (300 MHz, $CDCl_3$): δ 138.9, 136.5, 133.6, 115.6, 88.6, 72.0, 66.5, 43.6, 41.0, 32.7, 31.7. HRMS (EI) calcd for $C_{11}H_{16}O_2$ $[M]^+$ 180.1150, found 180.1129. IR (film): 3382, 2922, 2851, 1450, 1426, 1366, 1086, 1027, 923, 734 cm^{-1}.

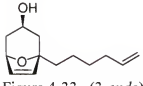


Figure 4-33. (3-*endo*)-1-Hex-5-enyl-8-oxabicyclo[3.2.1]oct-6-en-3-ol (**361**)

A solution of **344d** (1.0 g, 4.85 mmol) in THF (4.85 mL) was cooled to -78°C in a dry ice/acetone bath. L-selectride (1M in THF, 5.83 mL) was added dropwise and the reaction held at -78°C for one hour then allowed to warm slowly to room temperature. After an additional hour, the reaction was cooled to 0°C and a solution of 20% NaOH (5mL) and 30% H_2O_2 (2.5 mL) was added dropwise. After one hour, the solution was neutralized with 2M H_2SO_4. The aqueous layer was saturated with NaCl and extracted with ethyl acetate. The organic layers were combined, dried on $MgSO_4$, filtered and the solvent removed in vacuo. Purification by silica gel chromatography using gradient elution (96:4 hexane:ethyl acetate, 95:5; 92:8; 9:1; 85:5) (70:1 silica gel:crude) gave **361** as a colorless oil. R*f*=0.15 (3:2 hexane:ethyl acetate). ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.41 (1H, dd, J=5.9 Hz, 1.2 Hz), 6.23 (1H, d, J=5.9 Hz), 5.74-5.87 (1H, m), 4.91-5.03 (2H, m), 4.79-4.81 (1H, m), 4.01 (1H, m) 2.15-2.28 (2H, m), 2.00-2.10 (3H, m), 1.58-1.82 (5H, m), 1.35-1.49 (3H, m). ^{13}C NMR (300 MHz, $CDCl_3$): δ 139.0, 138.0, 136.2, 114.6, 85.7, 78.7, 66.0, 41.3, 37.3, 35.9, 33.9, 29.5, 23.4. HRMS (EI) calcd for $C_{13}H_{20}O_2$ $[M]^+$ 208.1463, found 208.1492. IR (film): 3437, 2935, 2859, 1726, 1348, 1110, 1074, 1033, 907, 871, 690 cm^{-1}.

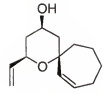


Figure 4-34. (2R*, 4R*, 6S*)-2-vinyl-1-oxaspiro[5.6]dodec-7-en-4-ol (**362**)

A solution of oxabicyclic alcohol **361** (18.0 mg, 0.087 mmol) in dichloromethane (7.65 mL) was prepared. A solution of **132** (1.5 mg, 0.002 mmol) in dichloromethane (1 mL) was added and the resulting solution allowed to stir under argon at room temperature. The reaction was monitored by TLC, using p-anisaldehyde as a stain. After 24 hours, evaporation under reduced pressure and purification of the residue by silica gel chromatography (100:1 silica gel: residue; 95:5 hexane: ethyl acetate) gave **362** as a colorless oil (8.7 mg, 48%). Unreacted starting material **361** (2.4 mg, 13 %) was recovered. R*f*=0.31 (3:2 hexane:ethyl acetate). ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.75-5.94 (2H, m), 5.55 (1H, d, J=11.6 Hz), 5.27 (1H, dt, J=17.4 Hz, 1.43 Hz), 5.12 (1H, dt, J= 10.5 Hz, 1.43 Hz), 3.92-4.08 (2H, m),1.93-2.28 (4H, m), 1.61-1.90 (5H, m), 1.42 (1H, bs), 1.20-1.40 (3H, m). ^{13}C NMR (300 MHz, $CDCl_3$): δ 139.5, 139.2, 131.7, 115.3, 78.3, 70.3, 65.4, 43.5, 41.2, 31.3, 27.5, 27.48, 24.1. HRMS (EI) calcd for $C_{13}H_{20}O_2$ $[M]^+$ 208.1463, found 208.1454. IR (film): 3353, 3016, 2926, 2853, 1726, 1646, 1453, 1029, 921, 757, 692 cm^{-1}.

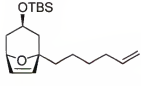


Figure 4-35. (3-*endo*)-*tert*-butyl-(1-hex-5-enyl-8-oxabicyclo[3.2.1]oct-6-en-3-yloxy)-dimethylsilane (**363**)

361 (0.58g, 2.80 mmol) and 2,6-lutidine (0.65 mL, 5.61 mmol) were dissolved in dichloromethane (2.80 mL) and cooled to 0°C. *tert*-butyldimethylsilyltrifluoromethane sulfonate (0.96 mL, 4.20 mmol) was added dropwise and the solution allowed to warm slowly to room temperature. After one hour, the solvent was removed *in vacuo* and the residue triturated with hexanes. The hexane layers were combined and evaporated under reduced pressure. Purification by silica gel chromatography (30:1 silica gel:crude; 97:3 hexane:ethyl acetate) gave **363** as a colorless oil (0.842g, 93.4%). R*f*=0.67 (3:2 hexane:ethyl acetate). ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.11 (1H, dd, J= 5.94 Hz, 1.67 Hz), 5.93 (1H, dd, J= 5.94 Hz, 0.71 Hz), 5.81 (1H, ddt, J=17.1 Hz, 10.2 Hz, 6.39 Hz), 4.91-5.03 (2H, m), 4.72-4.73 (1H, m), 4.06-4.10 (1H, m), 2.02-2.11 (3H, m), 1.91 (1H, dd, J= 5.47 Hz, 5.47 Hz), 1.29-1.66 (8H, m) 0.85 (9H, s), -0.29 (6H, s). ^{13}C NMR (300 MHz, $CDCl_3$): δ 139.2, 135.8, 133.9, 114.5, 85.6, 78.9, 65.3, 41.3, 37.7, 35.8, 33.9, 29.7, 25.9, 23.5, 18.0, -4.7. HRMS (EI) calcd, for $C_{19}H_{34}O_2Si$ $[M]^+$ 322.2328, found 322.2329. IR (film): 3077.4, 2934.5, 2856.7, 1641.1, 1472.1, 1463.0, 1253.4, 1081.9, 846.0, 773.6, 720.2 cm^{-1}.

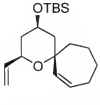


Figure 4-36. (2R*, 4R*, 6S*)-*tert*-butyl-dimethyl-(2-vinyl-1-oxa-spiro[5,6]dodec-7-en-4-yloxy)-silane (**364**)

A solution of oxabicyclic ether **363** (110.2 mg, 0.342 mmol) in dichloromethane (33.2 mL) was prepared. A solution of **132** (5.8 mg, 0.007 mmol) in dichloromethane (1 mL) was added and the resulting solution allowed to stir under argon at room temperature. The reaction was monitored by TLC, using p-anisaldehyde as a stain. After

16 hours, evaporation under reduced pressure and purification of the residue by silica gel chromatography (100:1 silica gel: residue; 100:0 hexane:ethyl acetate) gave **364** as a colorless oil (88.7 mg, 80.5%). R*f*=0.31 (9:1 hexane:ethyl acetate). ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.72-5.95 (2H, m), 5.25 (1H, ddd, J= 17.1 Hz, 1.4 Hz, 1.2 Hz), 5.10 (1H, ddd, J=10.5 Hz, 1.4 Hz, 1.2 Hz), 5.54 (1H, d, J=11.7 Hz), 3.88-4.10 (2H, m), 1.24-1.90 (12H, m), 0.90 (9H, s), 0.08 (6H, s). ^{13}C NMR (300 MHz, $CDCl_3$): δ 139.8, 139.5, 131.3, 115.1, 78.3, 70.6, 65.9, 43.7, 41.6, 31.3, 27.53, 57.52, 26.1, 25.9, 24.1, -4.7. HRMS (EI) calcd, for $C_{19}H_{34}O_2Si$ $[M]^+$ 322.2328, found 322.2330. IR (film): 3018, 2929, 2857, 1647, 1472, 1463, 1255, 1102, 1071, 836, 774 cm^{-1}.

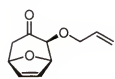


Figure 4-37. (2-*endo*)-2-allyloxy-8-oxabicyclo[3.2.1]oct-6-en-3-one (**367**)

α-hydroxy oxabicyclic ketone **366** (0.05g, 0.36 mmol) was dissolved in 0.36 mL of acetone. Anhydrous potassium carbonate (0.05g, 0.536 mmol) and allyl bromide (0.06 mL, 0.714 mL) were added and the mixture allowed to reflux under argon for forty-eight hours. Upon cooling, the potassium carbonate was filtered off. Evaporation under reduced pressure and purification by silica gel chromatography using gradient elution (100% hexane to 10% ethyl acetate:hexane) gave **367** as a pale yellow oil (25 mg; 39%). R_f = 0.44 (40% ethyl acetate: hexane). Starting ketone **366** was recovered (26 mg; 52%).

Figure 4-38. (2-*endo*)-2-methoxy-8-oxabicyclo[3.2.1]oct-6-en-3-one (**369**)

A solution of α-hydroxy oxabicyclic ketone **366** (0.1 g, 0.71 mmol) in 1 mL of dry THF was added dropwise to sodium hydride (16 mg, 0.68 mmol) in 0.71 mL of THF cooled to 0°C in an ice bath. The sodium hydride had been washed three times with pentanes and dried under argon prior to addition of **366**. The mixture was allowed to warm slowly to room temperature for one hour. It was once again cooled to 0°C and methyl iodide (0.05 mL, 0.82 mmol) was added dropwise. The mixture was then allowed to warm to room temperature. After 48 hours, the reaction was quenched by addition of water. The aqueous layer was extracted with ethyl acetate. The combined organic layer was then washed with brine, dried on $MgSO_4$ and filtered. Evaporation of the filtrate under reduced pressure and purification by silica gel chromatography (10% ether/hexane) gave **369** as a pale yellow oil (20 mg, 18%) R_f = 0.44 (25% ethyl acetate:hexane). ^1H NMR (300 MHz, $CDCl_3$): δ 6.31 (2H, s), 5.03 (2H, t, J = 5.1 Hz), 3.98 (1H, d, J = 5.1 Hz), 3.60 (3H, s), 2.78 (1H, dd, J = 15.3 Hz, 5.1 Hz), 2.38 (1H, d, J = 16.0 Hz). ^{13}C NMR (300MHz, $CDCl_3$): δ 204.8, 134.9, 131.7, 87.17, 79.5, 78.6, 60.0, 46.1.

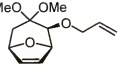


Figure 4:39. (2-*endo*)-2-allyloxy-3,3-dimethoxy-8-oxabicyclo[3.2.1]oct-6-ene (**371**)

A solution of α-hydroxy oxabicyclic ketal **365** (0.15 g, 0.81 mmol) in 1 mL of dry THF was added dropwise to sodium hydride (0.02 g, 0.89 mmol) in 1 mL of THF cooled to 0°C in an ice bath. The sodium hydride had been washed three times with pentanes and dried under argon prior to addition of **365**. The mixture was allowed to warm slowly to room temperature for one hour. It was then recooled to 0°C and allyl bromide (0.11 mL, 1.21 mmol) was added dropwise. The mixture was then allowed to warm to room

temperature. After 72 hours, the reaction was quenched by addition of water. The aqueous layer was extracted with ethyl acetate. The combined organic layer was then dried on $MgSO_4$ and filtered. Evaporation of the filtrate under reduced pressure and purification by silica gel chromatography gave **371** as a pale yellow oil (0.04 g, 22%) Starting ketal **365** was recovered (0.09 g, 60%). ^1H NMR (300 MHz, $CDCl_3$): δ 6.19-6.35 (2H, m), 5.97 (1H, ddt, J = 17.4 Hz, 10.2 Hz, 6.3 Hz), 5.30 (3H, m), 4.79 (1H, d, J = 17.4 Hz), 5.20 (1H, d, J = 10.2 Hz), 4.70-4.75 (2H, m), 4.17 (2H, d, J = 6.0 Hz), 3.76 (1H, d, J = 4 Hz), 3.28 (3H, s), 3.17 (3H, s), 2.00-2.05 (1H, m), 1.73-1.79 (1H, m). ^{13}C NMR (300MHz, $CDCl_3$): δ 135.0, 134.8, 132.7, 131.3, 83.0, 78.6, 78.0, 77.9, 72.2, 49.5, 48.9, 46.1, 34.1. IR (film): 2960, 2917, 2849, 1328, 1261, 1098, 1045, 962, 917, 826, 727 cm^{-1}.

Figure 4-40. (1R*, 6S*, 9R*)-7,7-dimethoxy-9-ethenyl-5,10-dioxabicyclo[4.4.0]dec-2-ene (**372**)

α-allyloxy bicyclic ketal **371** (0.03 g, 0.133 mmol) was dissolved in 12.3 mL of dry dichloromethane. A solution of catalyst **132** (2.29 mg, 0.0027 mmol) in 1 mL of dichloromethane was added and the reaction allowed to stir at room temperature for three hours. The reaction was monitored by TLC. Evaporation under reduced pressure and purification by silica gel chromatograpy using gradient elution (60% dichloromethane: pentane to 80% dichloromethane/19% pentane/1% ethyl acetate) gave **372** as a pale yellow oil (23.8 mg, 79%). ^1H NMR (300 MHz, $CDCl_3$): δ 6.02 (2H, s), 5.91 (1H, ddd, J = 17.4 Hz, 10.5 Hz, 6.5 Hz), 5.29 (1H, d, J = 17.4 Hz), 5.15 (1H, d, J = 10.5 Hz), 4.44

(1H, d, J = 16.8 Hz), 4.21 (1H, d, J = 15.6 Hz), 3.93-4.03 (2H, m), 3.45 (1H, s), 3.29 (3H, s), 3.25 (3H, s), 1.93 (1H, d, J = 13.2 Hz), 1.80 (1H, d, J = 13.2 Hz). ^{13}C NMR (300MHz, $CDCl_3$): δ 138.1, 131.6, 124.4, 116.5, 98.8, 74.7, 72.3, 67.6, 66.7, 47.8, 47.5, 33.9, 30.5, 29.9. IR (film): 2922, 1360, 1305, 1097, 1075, 707 cm^{-1}.

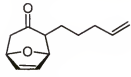


Figure 4-41. 2-pent-4-enyl-8-oxa-bicyclo[3.2.1]oct-6-en-3-one (**375**)

Trimethyl silyl enol ether **373** (1.0g, 5.09 mmol) was dissolved in 25.5 mL of THF in a dry 50 mL round bottom flask under argon and cooled to -78°C in a dry ice/acetone bath. Methyl lithium as a 1.6M solution in ether (4.77 mL, 7.64 mmol) was slowly added and the solution allowed to stir at -78°C for ca. 1.5 hours. 5-bromo-1-pentene (1.51mL, 12.73 mmol) dissolved in freshly distilled HMPA (12.73 mL) was added and the solution allowed to slowly warm to room temperature overnight. The solvent was then evaporated under reduced pressure. The residue was then redissolved in 50 mL of ether and extracted 15 times with 3 mL portions of water. The combined water layer was then back extracted 2 times with 3 mL portions of ether. The organic layer was then dried on $MgSO_4$ and filtered. Evaporation under reduced pressure and purification of the residue by silica gel chromatography (1:100 crude:silica gel; 3% ethyl acetate:hexane) gave **375** as a pale yellow oil (0.20 g, 20%) R_f= 0.48 (25% ethyl acetate:hexane). ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.26 (2H, s), 5.79 (1H, ddt, J = 16.9 Hz,10.2 Hz, 6.7 Hz), 4.94-5.05 (3H, m), 4.79 (1H, s), 2.66-2.83 (1H, m), 2.19-2.31 (2H, m), 2.04-2.10 (2H, m), 1.7-1.9 (2H, m), 1.4-1.6 (2H, m). ^{13}C NMR (300MHz, $CDCl_3$): δ 208.8, 207.1, 138.5, 138.4, 134.8, 133.9, 133.6, 132.0, 115.2, 115.1, 80.6, 80.5, 78.3, 77.7, 57.0, 56.2, 46.1, 45.3, 34.0, 33.7,

29.8, 26.8, 26.8, 25.1; HRMS (EI) calcd for $C_{12}H_{16}O_2$ $[M]^+$ 192.1150, found 192.1152. IR (film): 3077, 2940, 2862, 1713, 1641, 1460, 1409, 1336, 1179, 1046, 962, 913, 716 cm^{-1}, Anal. Calcd. for $C_{12}H_{16}O_2$: C, 74.97; H, 8.39. Found: C, 75.01; H, 8.40.

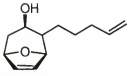
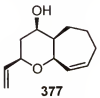


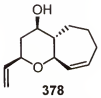
Figure 4-42. (3-*endo*)-2-pent-4-enyl-8-oxabicyclo[3.2.1]oct-6-en-3-ol (**376**)

α-substituted oxabicylic ketone **375** (0.14 g, 0.73 mmol) was dissolved in 0.73 mL THF and cooled to -78°C in a dry ice/acetone bath. L-selectride as a 1M solution in THF (0.87 mL, 0.87 mmol) was added dropwise and the solution stirred at -78°C for one hour. The solution was then allowed to warm slowly to room temperature, ca. 3 hours. The reaction was monitored by TLC. Upon completion, the solution was cooled to 0°C, and 1 mL of a 2:1 mixture of 20% NaOH and 30% H_2O_2 was added. The reaction was allowed to warm slowly to room temperature with stirring. The mixture was then neutralized with 2M H_2SO_4. The aqueous layer was saturated with NaCl and then extracted with ethyl acetate. The combined organic layer was dried on $MgSO_4$ and filtered. Evaporation under reduced pressure and purification of the residue by silica gel chromatography using gradient elution (15% ether:hexane to 40% ether:hexane) gave **376** as a colorless oil (0.104g, 74%). R_f = 0.26 (40% ethyl acetate:hexane). ^1H NMR (300 MHz, $CDCl_3$): δ 6.49 (1H, s), 6.13 (1H, s), 5.74-5.91 (1H, m), 4.93-5.06 (2H, m), 4.53-4.78 (2H, m), 3.90-4.09 (1H, m), 2.20-2.28 (1H, m), 2.05-2.14 (3H, m), 1.19-1.81 (6H, m). ^{13}C NMR (300MHz, $CDCl_3$): δ 139.0, 138.8, 137.2, 135.2, 131.6, 131.3, 114.8, 114.7, 81.5, 80.2, 78.1, 78.0, 67.7, 66.0, 43.8, 40.1, 36.1, 34.3, 32.6, 27.4, 27.0, 26.3, 23.6; HRMS (EI)

calcd for $C_{12}H_{18}O_2$ $[M]^+$ 194.1307, found 194.1306. IR (film): 3444, 3076, 2937, 1640, 1439, 1346, 1113, 1048, 911, 702 cm^{-1}.



377



378

Figure 4-43. (1R*, 7R*, 8R*, 10R*)-10-ethenyl-11-oxabicyclo[4.5.0]undec-2-en-8-ol (**377**) and (1R*, 7S*, 8R*, 10R*)-10-ethenyl-11-oxabicyclo[4.5.0]undec-2-en-8-ol (**378**)

A 64:36 *exo*:*endo* mixture of oxabicyclic alcohols **376** (60 mg, 0.31 mmol) was dissolved in 29 mL of dichloromethane under argon. A solution of **132** (5.25 mg, 0.006 mmol) in 2 mL of dichloromethane was added and the reaction stirred at room temperature. The reaction was monitored by TLC. After 2 hours, evaporation of the solvent under reduced pressure and purification of the residue by silica gel chromatography using gradient elution (5% ether:hexane to 15% ether:hexane) gave **377** as a colorless oil (10 mg, 46%) and **378** as a colorless oil (10 mg, 25%).

(377) ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.89 (1H, dd, J = 17.4 Hz, 10.46 Hz), 5.70-5.79 (1H, m), 5.62 (1H, dt, J = 12.36 Hz, 2.4 Hz), 5.30 (1H, dt, J = 17.4 Hz, 2.4 Hz), 5.13 (1H, dt, J= 10.5 Hz, 1.6 Hz), 4.31 (2H, d, J = 10.5 Hz), 4.00 (1H, m), 2.16-2.27 (1H, m), 1.9-2.0 (1H, m), 1.3-1.8 (9H, m). ^{13}C NMR (300MHz, $CDCl_3$): δ 139.3, 135.5, 129.0, 115.2, 76.0, 71.4, 70.3, 44.6, 39.5, 32.0, 29.4, 27.1; HRMS (EI) calcd for $C_{12}H_{18}O_2$ $[M]^+$ 194.1307, found 194.1303.

(378) ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.85-5.97 (2H, m), 5.71 (1H, dddd, J = 11.9 Hz, 6.2 Hz, 1.9 Hz, 1.2 Hz), 5.26 (1H, dt, J = 17.4 Hz, 1.4 Hz), 5.26 (1H, dt, J = 17.4 Hz, 1.4 Hz), 5.13 (1H, dt, J= 10.5 Hz, 1.2 Hz), 3.87-4.00 (3H, m), 2.10-2.34 (3H, m), 1.45-

2.20 (8H, m). ^{13}C NMR (300MHz, $CDCl_3$): δ 138.6, 134.9, 128.2, 115.7, 71.4, 44.1, 35.9, 28.5, 26.9, 20.8; HRMS (EI) calcd for $C_{12}H_{18}O_2$ $[M]^+$ 194.1307, found 194.1306.

Figure 4-44. 2-allyl-8-oxa-bicyclo[3.2.1]oct-6-en-3-one (**386**)

Trimethyl silyl enol ether **373** (0.23g, 1.2 mmol) was dissolved in 5.1 mL of THF in a dry 10 mL round bottom flask under argon and cooled to -78°C in a dry ice/acetone bath. Methyl lithium as a 1.6M solution in ether (1.08 mL, 1.72 mmol) was slowly added and the solution allowed to stir at -78°C for ca. 1.5 hours. Allyl bromide (0.25 mL, 2.87 mmol) dissolved in freshly distilled HMPA (2.87 mL) was added and the solution allowed to slowly warm to room temperature overnight. The solvent was then evaporated under reduced pressure. The residue was then redissolved in 30 mL of ether and extracted 15 times with 1 mL portions of water. The combined water layer was then back extracted 2 times with 1 mL portions of ether. The organic layer was then dried on $MgSO_4$ and filtered. Evaporation under reduced pressure and purification of the residue by silica gel chromatography (1:100 crude:silica gel; 3% ethyl acetate:hexane) gave **386** as a mixture of *exo* and *endo* isomers (65:35) as a pale yellow oil (0.05 g, 26%). R_f = 0.40 (3:1 hexane:ethyl acetate). ^1H NMR (300 MHz, $CDCl_3$): δ 6.24-6.30 (2H, m), 5.72-5.86 (1H, m), 5.09-5.18 (1H, m), 5.00 (1H, d, J=4.8 Hz), 4.83 (1H, s), 2.78 (2H, dd, J=16.5 Hz, 4.8 Hz), 2.42-2.61 (2H, m), 2.25-2.31 (2H, m). ^{13}C NMR (300MHz, $CDCl_3$): δ 208.3, 135.1, 134.1, 133.5, 117.9, 79.5, 77.6, 55.7, 45.3, 34.7; HRMS (EI) calcd for $C_{10}H_{12}O_2$ $[M]^+$ 164.0837, found 164.0836. IR (film): 3079, 2961, 1714, 1641, 1442,

1410, 1338, 1177, 967, 920, 716 cm^{-1}, Anal. Calcd. for $C_{10}H_{12}O_2$: C, 73.15; H, 7.37. Found: C, 73.12; H, 7.52.

Figure 4-45. (3-*endo*)-2-allyl-8-oxabicyclo[3.2.1]oct-6-en-3-ol (**387**)

α-substituted oxabicylic ketone **386** (68 mg, 0.41 mmol) was dissolved in 0.41 mL THF and cooled to -78°C in a dry ice/acetone bath. L-selectride as a 1M solution is THF (0.5 mL, 0.5mmol) was added dropwise and the solution stirred at -78°C for one hour. The solution was then allowed to warm slowly to room temperature, ca. 3 hours. The reaction was monitored by TLC. Upon completion, the solution was cooled to 0°C, and 0.5 mL of a 2:1 mixture of 20% NaOH and 30% H_2O_2 were added. The reaction was allowed to warm slowly to room temperature with stirring. The mixture was then neutralized with 2M H_2SO_4. The aqueous layer was saturated with NaCl and then extracted with ethyl acetate. The combined organic layer was dried on $MgSO_4$ and filtered. Evaporation under reduced pressure and purification of the residue by silica gel chromatography using gradient elution (15% ether:hexane to 40% ether:hexane) gave **387** as a colorless oil (0.028g, 41%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.49 (1H, s), 6.11-6.16 (1H, m), 5.76-5.94 (1H, m), 5.02-5.21 (2H, m), 4.56-4.78 (2H, m), 1.62-2.56 (7H, m). ^{13}C NMR (300MHz, $CDCl_3$): δ 137.6, 137.1, 136.4, 134.9, 131.7, 131.3, 116.9, 80.9, 80.1, 78.2, 78.1, 78.0, 67.8, 66.0, 43.8, 39.9, 36.0, 32.7, 32.6, 29.3.

Figure 4-46. (1R*, 5R*, 6R*, 8R*)-8-ethenyl-9-oxabicyclo[4.3.0]non-2-en-6-ol (**388**)

A 65:35 *exo*:*endo* mixture of oxabicyclic alcohols **387** (24 mg, 0.144 mmol) was dissolved in 13.4 mL of dichloromethane under argon. A solution of **132** (2.45 mg, 0.003 mmol) in 1 mL of dichloromethane was added and the reaction stirred at room temperature. The reaction was monitored by TLC. After 2 hours, evaporation of the solvent under reduced pressure and purification of the residue by silica gel chromatography using gradient elution (5% ether:hexane to 15% ether:hexane) gave **388** as a colorless oil (3.2 mg, 38%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.20-6.23 (1H, m), 5.97-6.01 (1H, m), 5.87 (1H, dd, J = 17.2 Hz, 10.5 Hz), 5.25 (1H, dt, J = 17.2 Hz, 1.43 Hz), 5.13 (1H, dt, J = 10.5 Hz, 1.43 Hz), 4.46-4.49 (1H, m), 4.18 (1H, s), 3.82-3.89 (1H, m), 2.25-2.49 (3H, m), 1.85-1.92 (1H, m), 1.50-1.53 (2H, m). ^{13}C NMR (300MHz, $CDCl_3$): δ 138.7, 138.0, 131.4, 115.8, 81.2, 75.3, 68.8, 43.9, 36.4, 30.5.

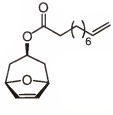


Figure 4-47. (3-*endo*)-Dec-9-enoic acid 8-oxabicyclo[3.2.1]oct-6-en-3-yl ester (**393**)

In a dry 10 mL round bottom flask under argon, 9-decenoic acid (0.5g, 2.94 mmol) was dissolved in ca. 3.0 mL of dry THF. Triethyl amine (0.41 mL, 2.94 mmol) and 2,4,6-trichlorobenzoyl chloride (0.46 mL, 2.94 mmol) were added and the solution was allowed to stir at room temperature under argon for 2 hours. The solvent was then

evaporated under argon, leaving a white solid. A solution of alcohol **390** (0.37g, 2.94 mmol) and DMAP (0.718g, 5.9 mmol) in benzene was added to the white solid and allowed to stir under argon overnight. The reaction mixture was then diluted with ether, washed successively with 1% HCl, saturated $NaHCO_3$ and water, dried on $MgSO_4$ and filtered. Evaporation under reduced pressure and purification of the residue by silica gel chromatograpy (1:40 crude:silica gel; 5% ether:hexane) gave **393** as a colorless oil (0.54 g, 66%); R_f = 0.58 (40% ethyl acetate: hexane). ^1H NMR (300 MHz, $CDCl_3$): δ 6.24 (2H, s), 5.81 (1H, ddt, J = 17.2 Hz, 10.2 Hz, 6.72 Hz), 4.91-5.08 (3H, m), 4.70 (2H, d, J = 4.2 Hz), 2.21-2.31 (4H, m), 2.04 (2H, dd, J=18.0 Hz, 6.72 Hz), 1.6 (4H, d, J = 15.5 Hz), 1.26-1.43 (3H, m). ^{13}C NMR (300MHz, $CDCl_3$): δ173.1, 139.2, 133.7, 118.2, 114.4, 77.5, 66.7, 35.0, 33.9, 32.6, 29.3, 29.27, 29.1, 29.05, 25.2. Anal. Calcd. for $C_{17}H_{26}O_3$: C, 73.34; H, 9.41. Found: C, 73.06; H, 9.45.

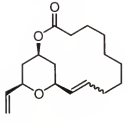


Figure 4-48. (1R*, 13S*, 15R*)-15-vinyl-2,14-dioxa-bicyclo[11.3.1]heptadec-11-en-3-one (**396**)

Oxabicyclic ester **393** (0.21 g, 0.77 mmol) was dissolved in 75 mL of dry dichloromethane. A solution of catalyst **132** (16.4 mg, 0.019 mmol) in 2 mL of dichloromethane was added and the reaction allowed to stir at room temperature for three hours. The reaction was monitored by TLC. Evaporation under reduced pressure gave a reddish brown crude residue containing *cis/trans* mixtures of **396** (0.15g, 70%).

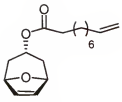


Figure 4-49. (3-*exo*)-Dec-9-enoic acid 8-oxabicyclo[3.2.1]oct-6-en-3-yl ester (**394**)

In a dry 10 mL round bottom flask under argon, 9-decenoic acid (0.35 g, 2.03 mmol) was dissolved in ca. 2.0 mL of dry THF. Triethyl amine (0.28 mL, 2.03 mmol) and 2,4,6-trichlorobenzoyl chloride (0.32 mL, 2.03 mmol) were added and the solution was allowed to stir at room temperature under argon for 2 hours. The solvent was then evaporated under argon, leaving a white solid. A solution of alcohol **391** (0.25 g, 2.03 mmol) and DMAP (0.49 g, 3.97 mmol) in benzene was added to the white solid and allowed to stir under argon overnight. The reaction mixture was then diluted with ether, washed successively with 1% HCl, saturated $NaHCO_3$ and water, dried on $MgSO_4$ and filtered. Evaporation under reduced pressure and purification of the residue by silica gel chromatograpy (1:40 crude:silica gel; 10% ether:hexane) gave **394** as a colorless oil (0.38 g, 67%); R_f = 0.66 (40% ethyl acetate: hexane). ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.22 (2H, s), 5.81 (1H, ddt, J = 17.1 Hz, 10.2 Hz, 6.6 Hz), 4.91-5.08 (3H, m), 4.70 (2H, d, J = 3.6 Hz), 2.21-2.31 (4H, m), 2.01-2.08 (2H, m), 1.57-1.63 (4H, m), 1.31-1.44 (2H, m). ^{13}C NMR (300MHz, $CDCl_3$): δ 173.1, 139.3, 133.8, 114.4, 77.5, 66.7, 35.0, 33.9, 32.6, 29.3, 29.27, 29.1, 29.0, 25.2; IR (film): 3076, 2927, 2855, 1728, 1640, 1463, 1346, 1218, 1175, 703 cm^{-1}, Anal. Calcd. for $C_{17}H_{26}O_3$: C, 73.34; H, 9.41. Found: C, 73.27; H, 9.41.

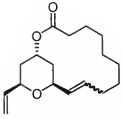


Figure 4-50. (1S*, 13S*, 15R*)-15-vinyl-2,14-dioxa-bicyclo[11.3.1]heptadec-11-en-3-one (**398**)

Oxabicyclic ester **393** (0.07 g, 0.25 mmol) was dissolved in 23 mL of dry dichloromethane. A solution of catalyst **132** (4.28 mg, 0.005 mmol) in 2 mL of dichloromethane was added and the reaction allowed to stir at room temperature for one hour. The reaction was monitored by TLC. Evaporation under reduced pressure gave a reddish brown crude residue containing *cis/trans* mixtures of **398** (0.063 g, 76%).

APPENDIX
SELECTED SPECTRA

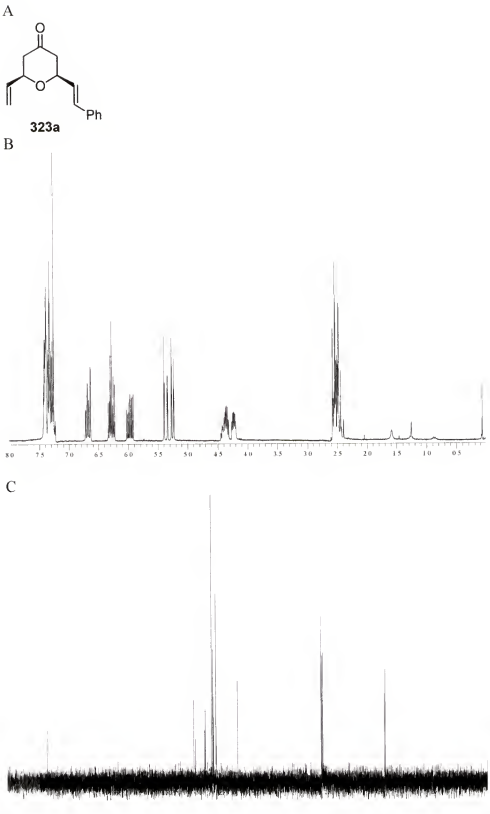
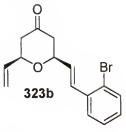


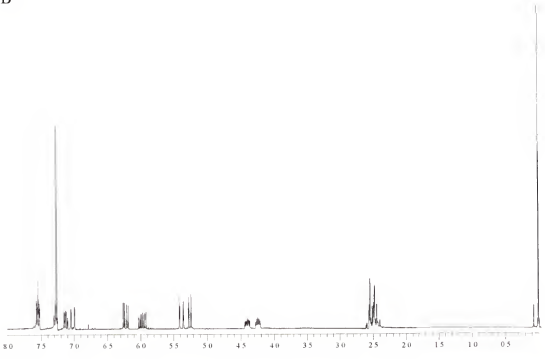
Figure A-1. Spectroscopy data for **323a**. A) Structure B) ^{1}H spectrum C) ^{13}C spectrum

A



323b

B



C

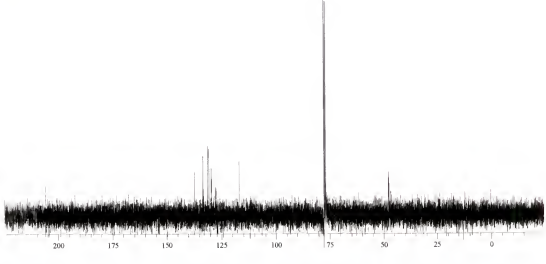
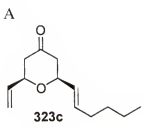
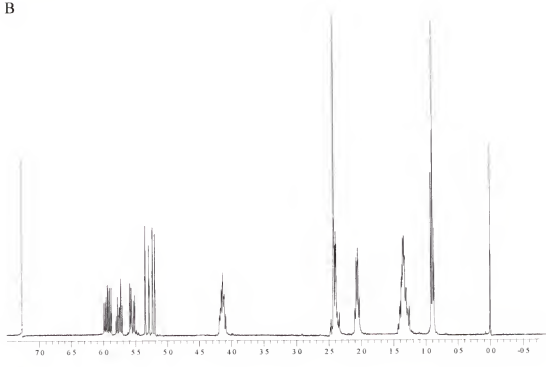


Figure A-2. Spectroscopy data for **323b**. A) Structure B) ^{1}H spectrum C) ^{13}C spectrum





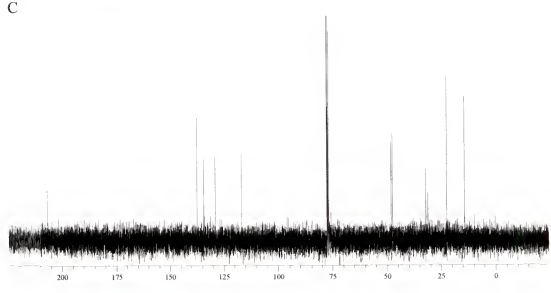


Figure A-3. Spectroscopy data for **323c**. A) Structure B) ^{1}H spectrum C) ^{13}C spectrum

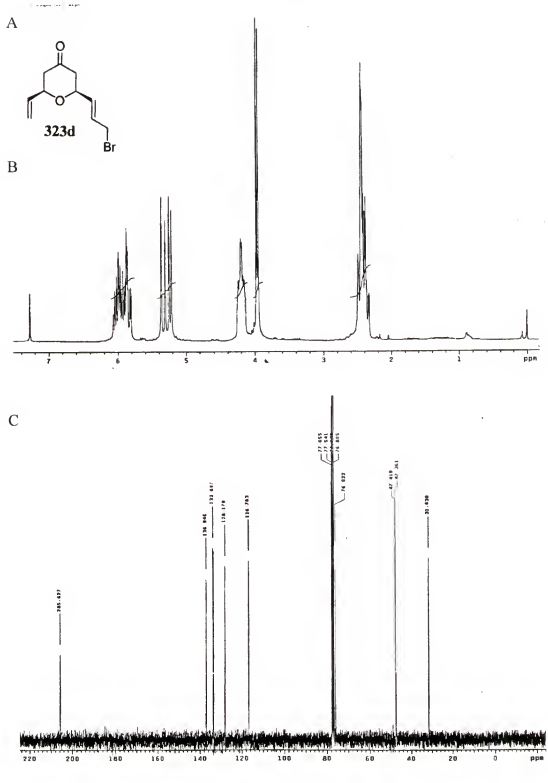


Figure A-4. Spectroscopy data for **323d**. A) Structure B) ^{1}H spectrum C) ^{13}C spectrum

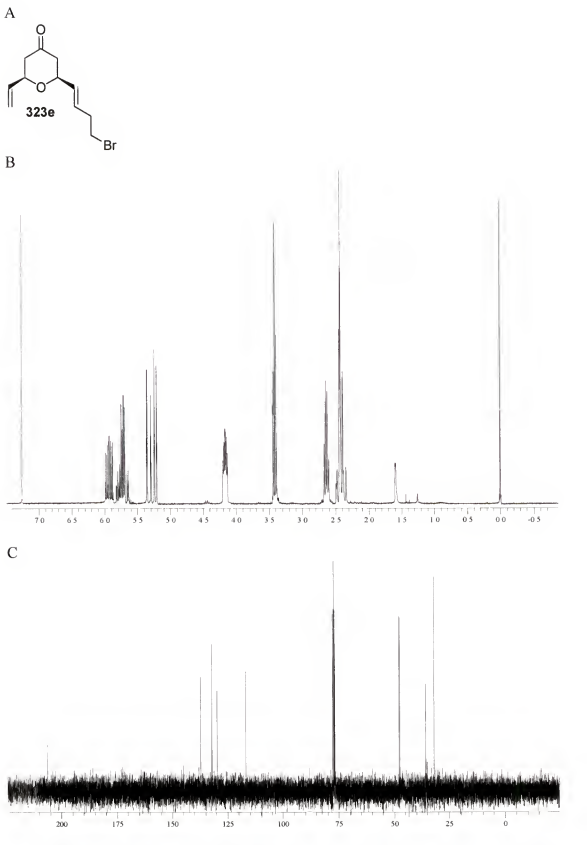
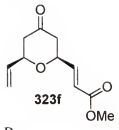


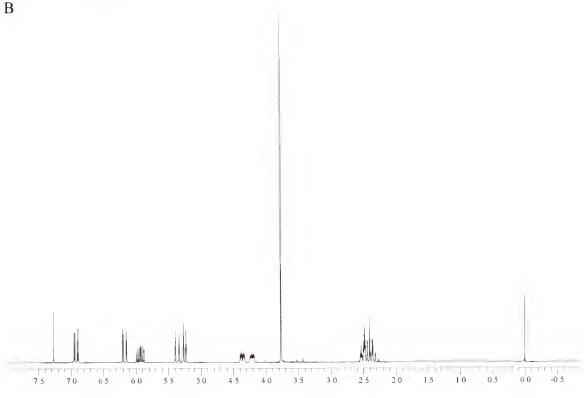
Figure A-5. Spectroscopy data for **323e**. A) Structure B) ^{1}H spectrum C) ^{13}C spectrum

A



323f

B



C

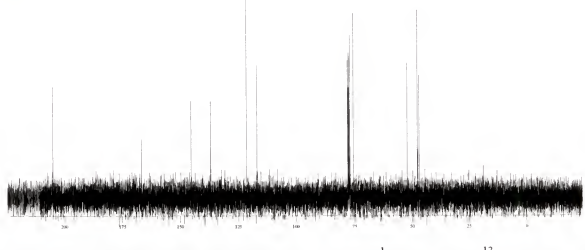


Figure A-6. Spectroscopy data for **323f**. A) Structure B) ^{1}H spectrum C) ^{13}C spectrum

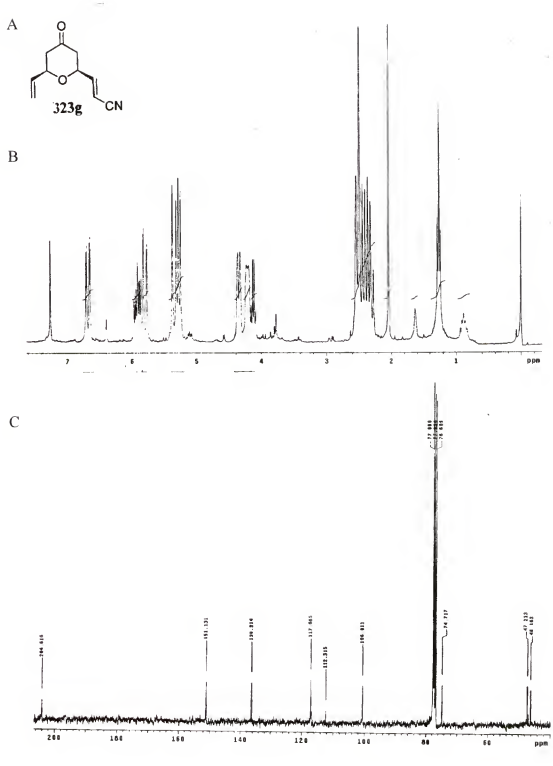


Figure A-7. Spectroscopy data for **323g**. A) Structure B) ^{1}H spectrum C) ^{13}C spectrum

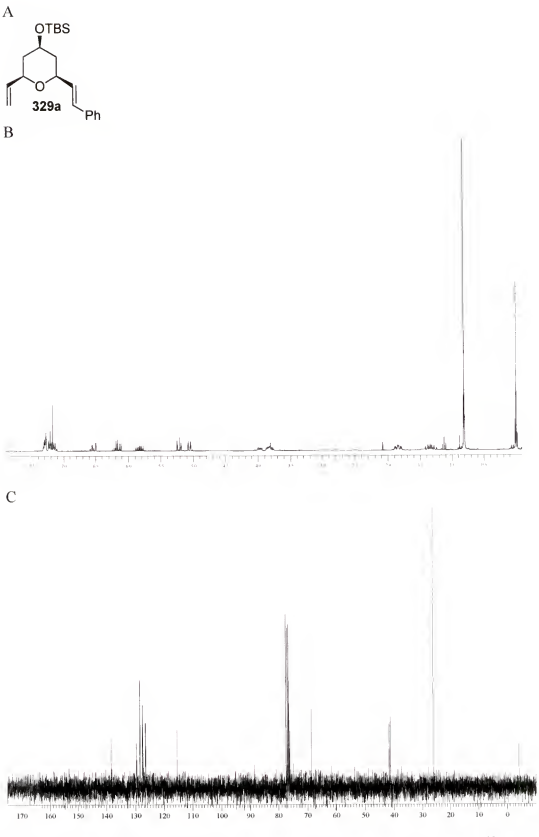


Figure A-8. Spectroscopy data for **329a**. A) Structure B) ^{1}H spectrum C) ^{13}C spectrum

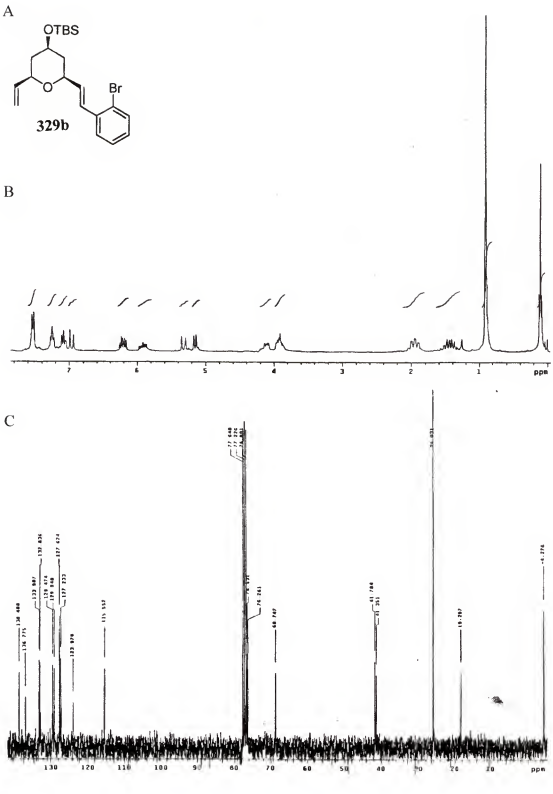


Figure A-9. Spectroscopy data for **329b**. A) Structure B) ^{1}H spectrum C) ^{13}C spectrum

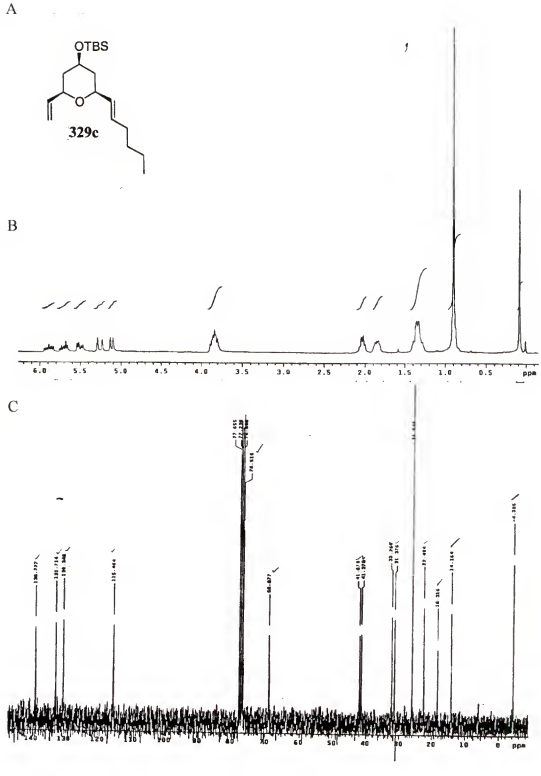


Figure A-10. Spectroscopy data for **329c**. A) Structure B) ^{1}H spectrum C) ^{13}C spectrum

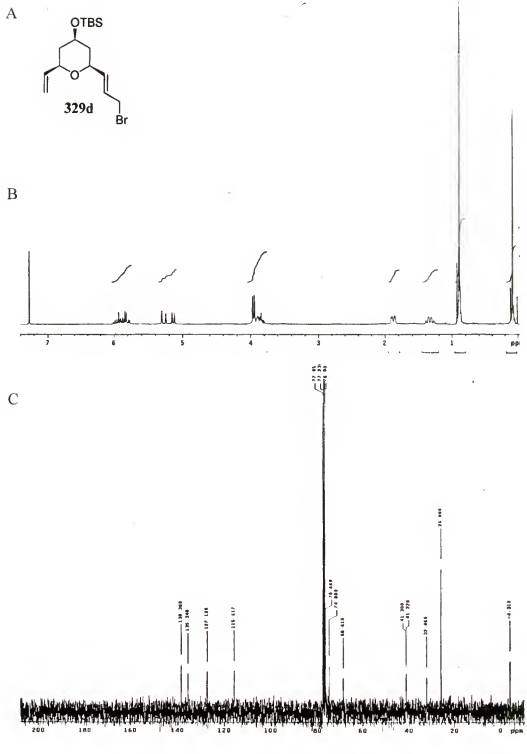


Figure A-11. Spectroscopy data for **329d**. A) Structure B) ^{1}H spectrum C) ^{13}C spectrum

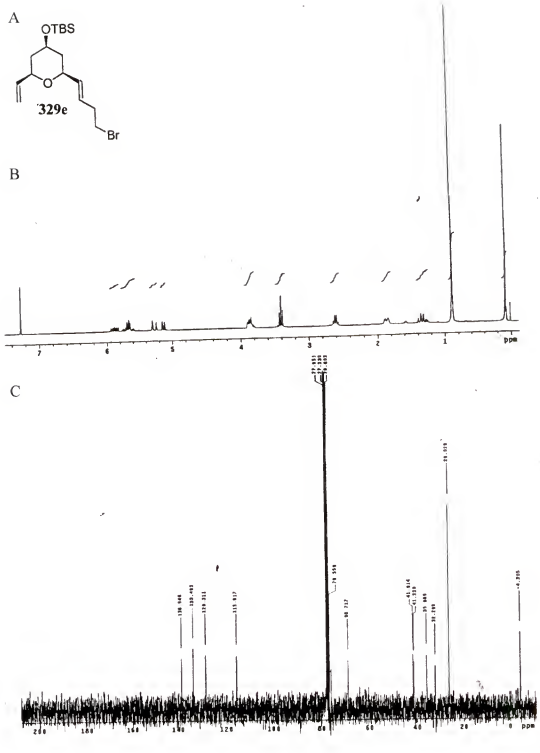


Figure A-12. Spectroscopy data for **329e**. A) Structure B) ^{1}H spectrum C) ^{13}C spectrum

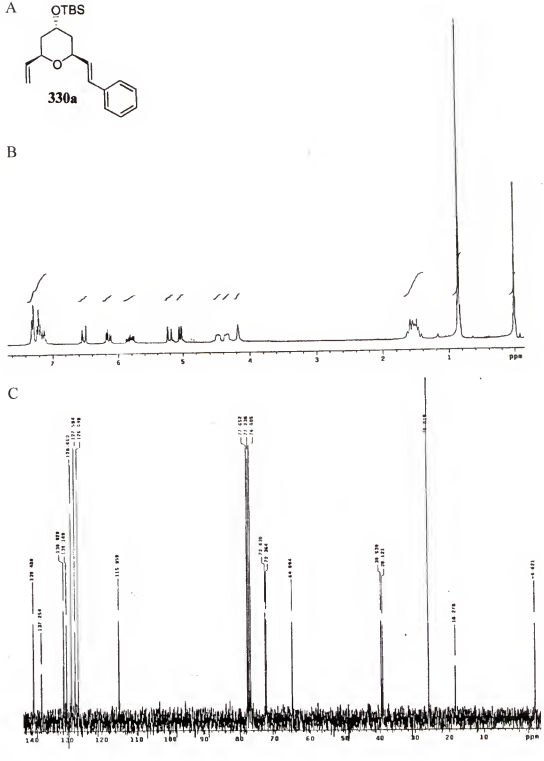


Figure A-13. Spectroscopy data for **330a**. A) Structure B) ^{1}H spectrum C) ^{13}C spectrum

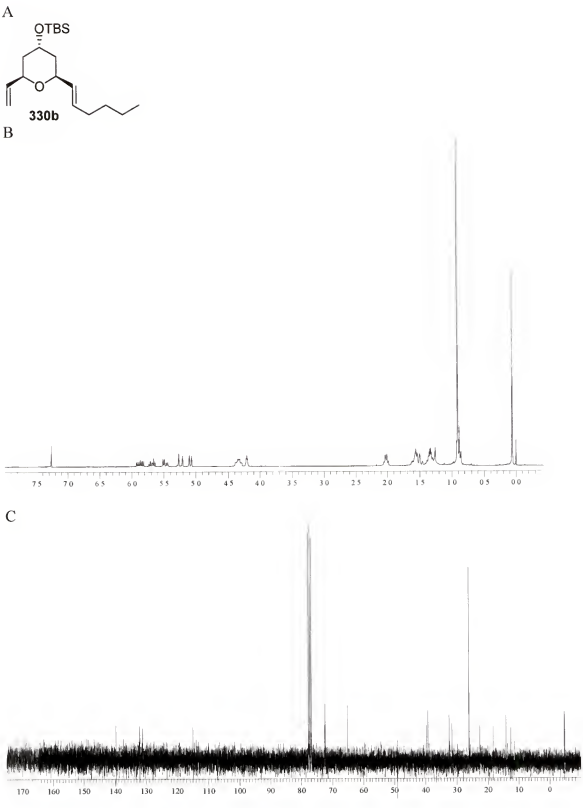
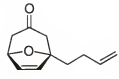


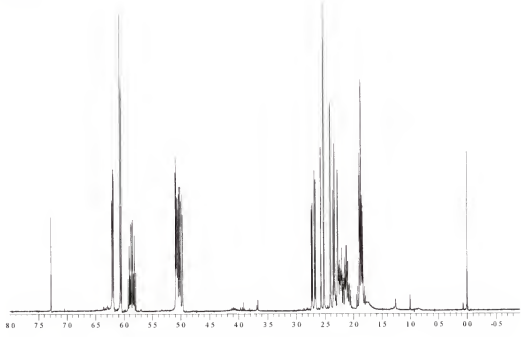
Figure A-14. Spectroscopy data for **330b**. A) Structure B) ^{1}H spectrum C) ^{13}C spectrum

A



344a

B



C

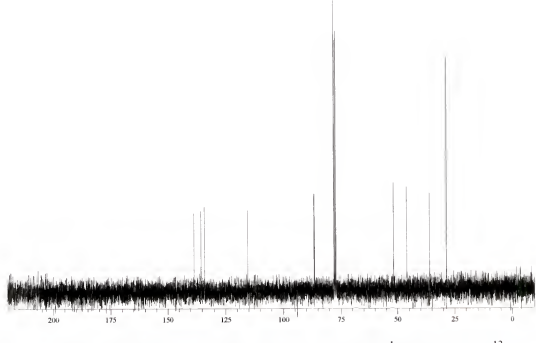
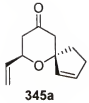


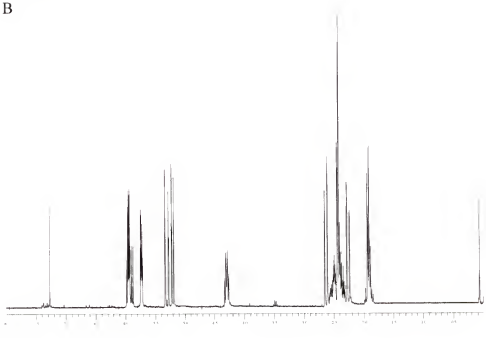
Figure A-15. Spectroscopy data for **344a**. A) Structure B) ^{1}H spectrum C) ^{13}C spectrum

A



345a

B



C

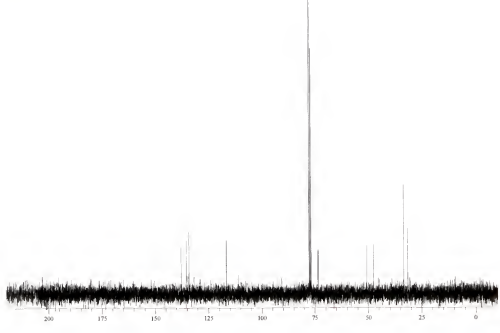
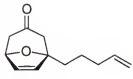


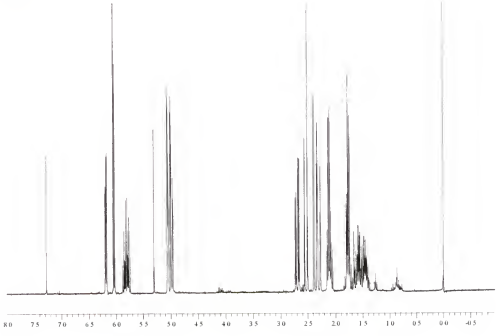
Figure A-16. Spectroscopy data for **345a**. A) Structure B) ^{1}H spectrum C) ^{13}C spectrum

A



344b

B



C

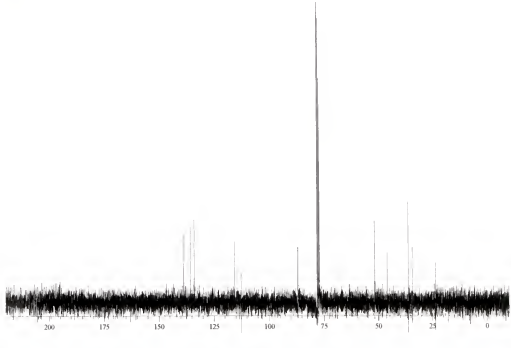
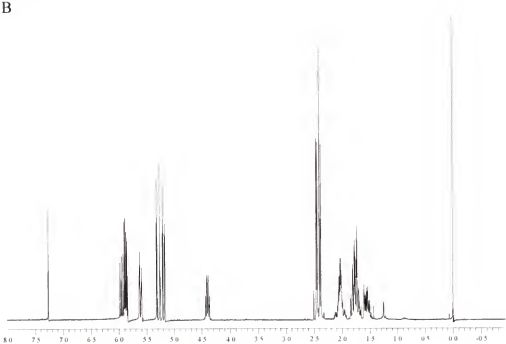


Figure A-17. Spectroscopy data for **344b**. A) Structure B) ^{1}H spectrum C) ^{13}C spectrum

A

345b

B



C

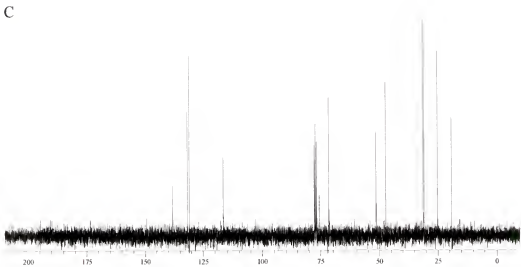
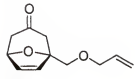


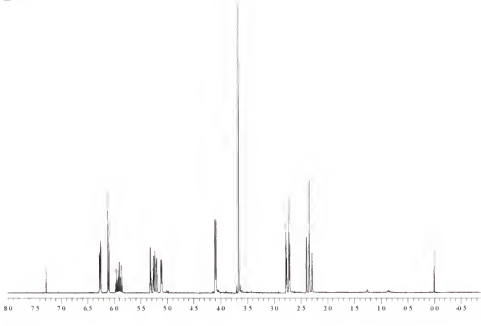
Figure A-18. Spectroscopy data for **345b**. A) Structure B) ^{1}H spectrum C) ^{13}C spectrum

A



344c

B



C

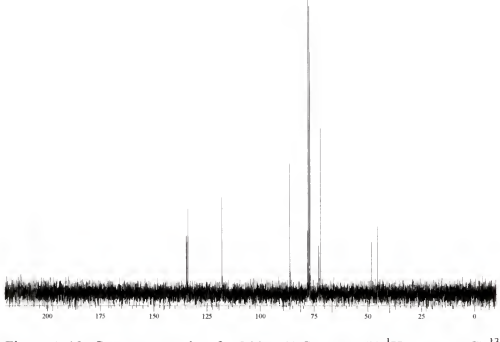


Figure A-19. Spectroscopy data for **344c**. A) Structure B) ^{1}H spectrum C) ^{13}C spectrum

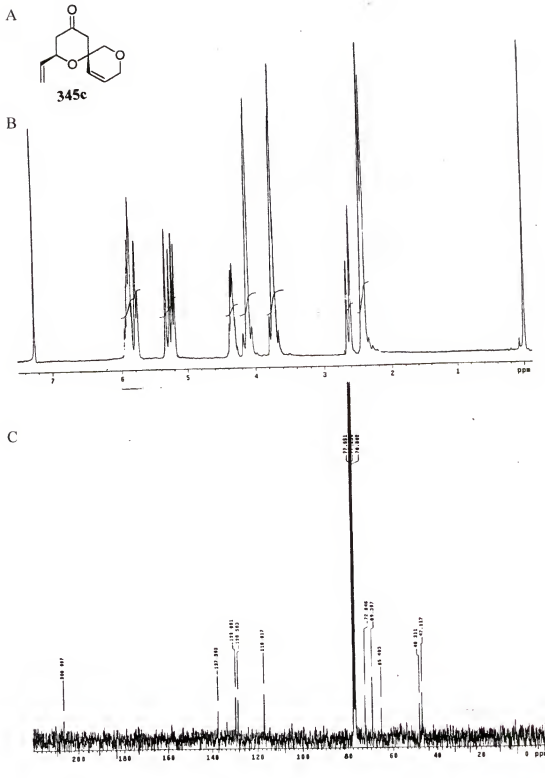


Figure A-20. Spectroscopy data for **345c**. A) Structure B) ^{1}H spectrum C) ^{13}C spectrum

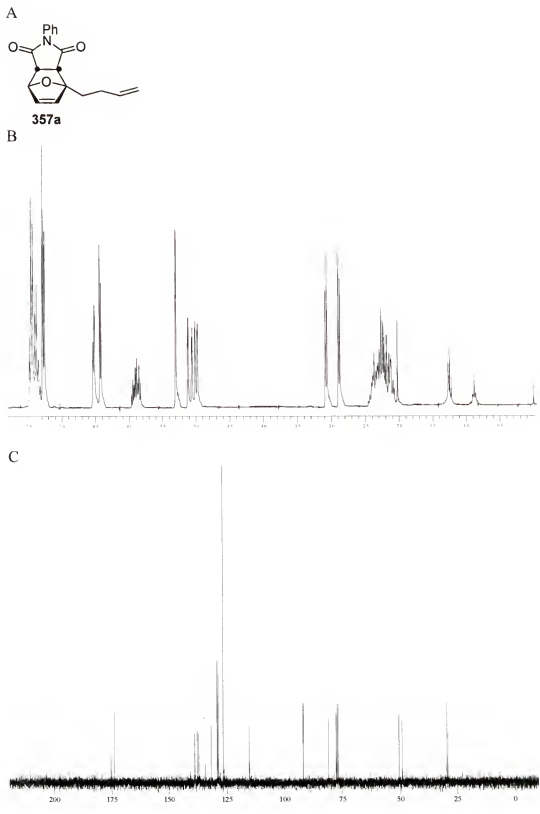
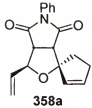


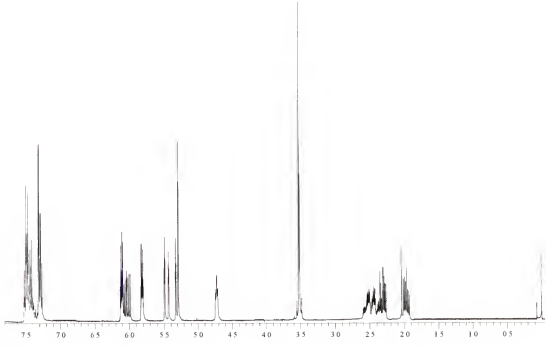
Figure A-21. Spectroscopy data for **357a**. A) Structure B) ^{1}H spectrum C) ^{13}C spectrum

A



358a

B



C

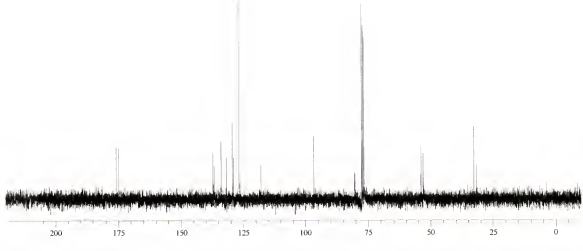
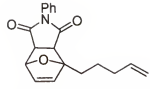


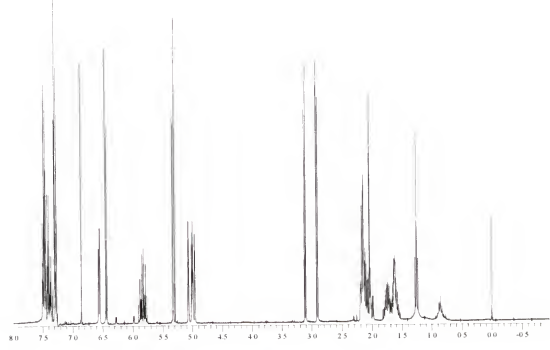
Figure A-22. Spectroscopy data for **358a**. A) Structure B) ^{1}H spectrum C) ^{13}C spectrum

A



357b

B



C

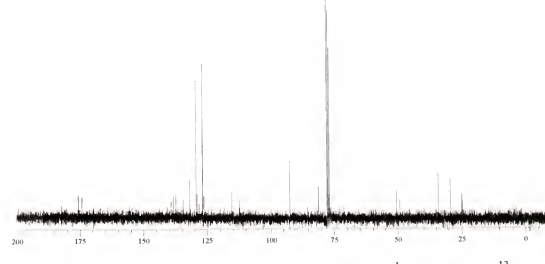
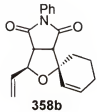


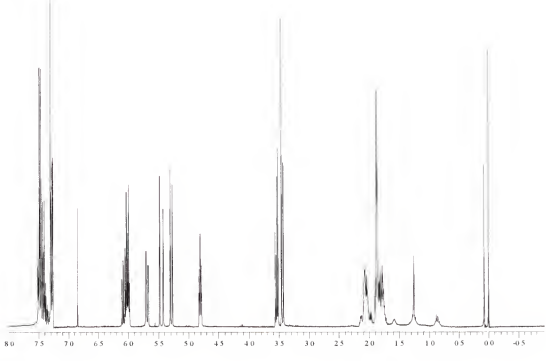
Figure A-23. Spectroscopy data for **357b**. A) Structure B) ^{1}H spectrum C) ^{13}C spectrum

A



358b

B



C

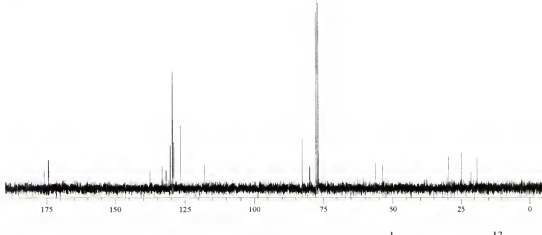
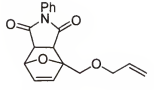


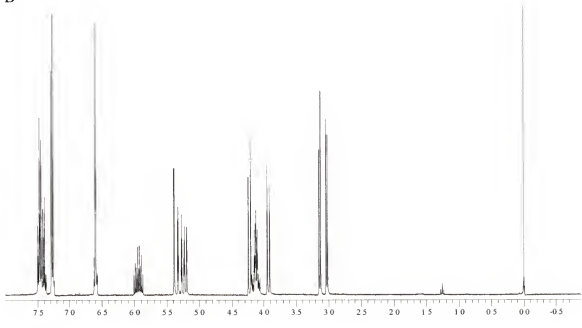
Figure A-24. Spectroscopy data for **358b**. A) Structure B) ^{1}H spectrum C) ^{13}C spectrum

A



357c

B



C

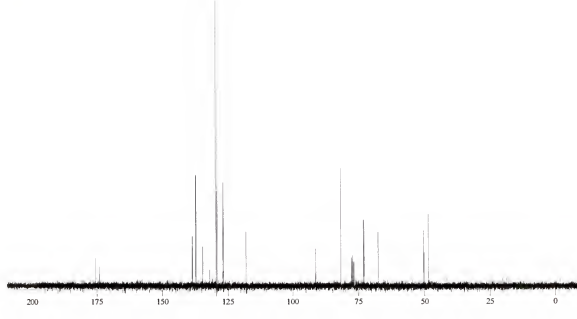
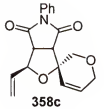


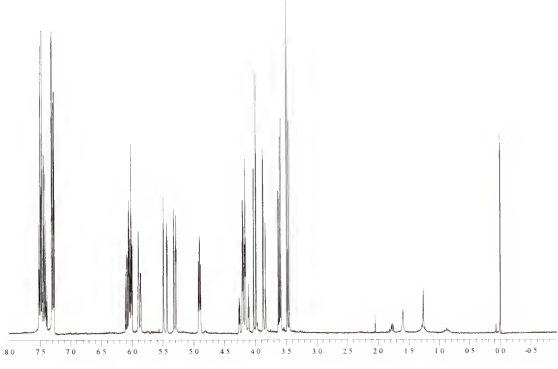
Figure A-25. Spectroscopy data for **357c**. A) Structure B) ^{1}H spectrum C) ^{13}C spectrum

A



358c

B



C

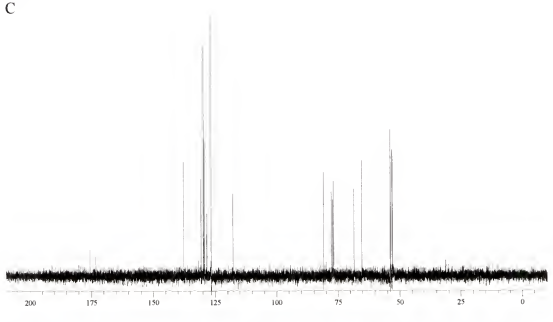
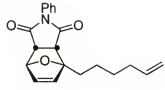


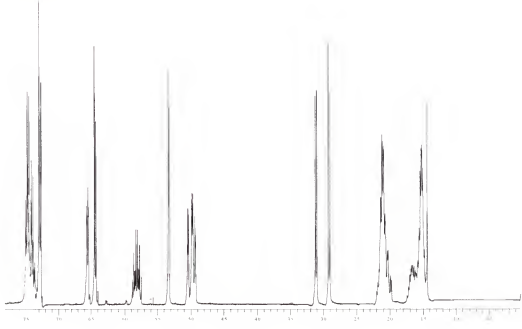
Figure A-26. Spectroscopy data for **358c**. A) Structure B) ^{1}H spectrum C) ^{13}C spectrum

A



357d

B



C

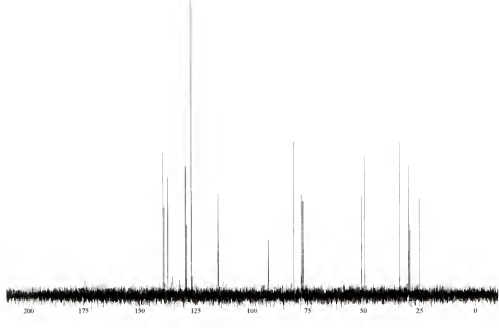


Figure A-27. Spectroscopy data for **357d**. A) Structure B) ^{1}H spectrum C) ^{13}C spectrum

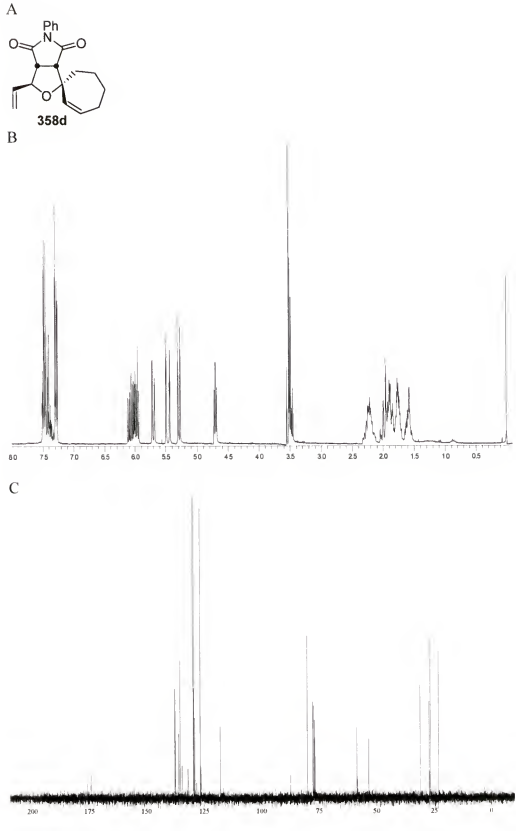


Figure A-28. Spectroscopy data for **358d**. A) Structure B) ^{1}H spectrum C) ^{13}C spectrum

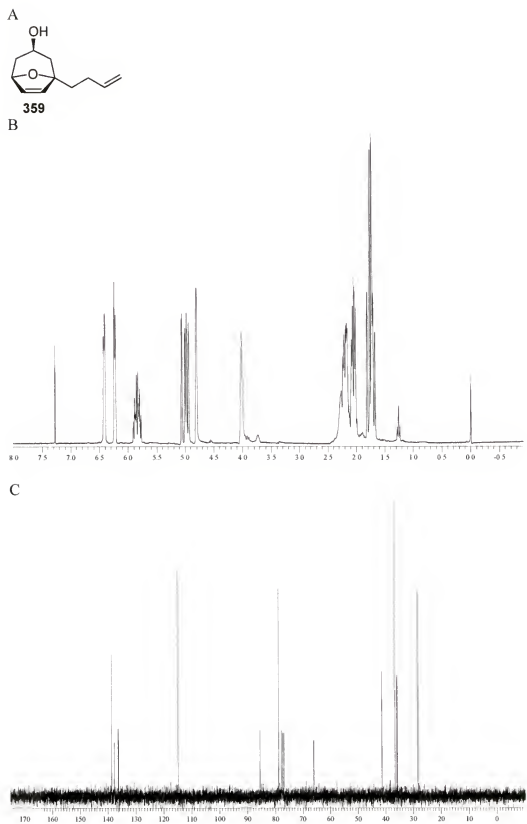
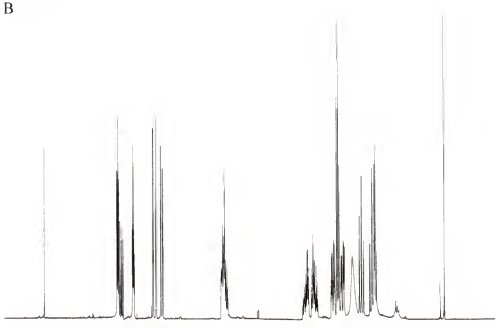


Figure A-29. Spectroscopy data for **359**. A) Structure B) ^{1}H spectrum C) ^{13}C spectrum

A

360

B



C

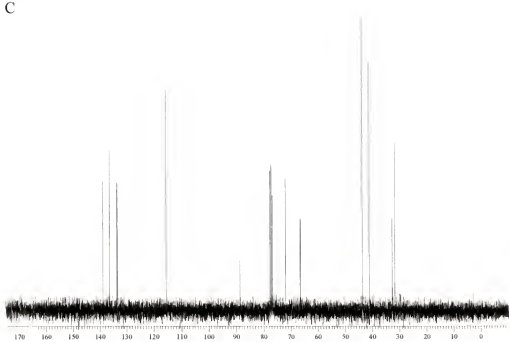
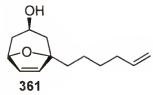


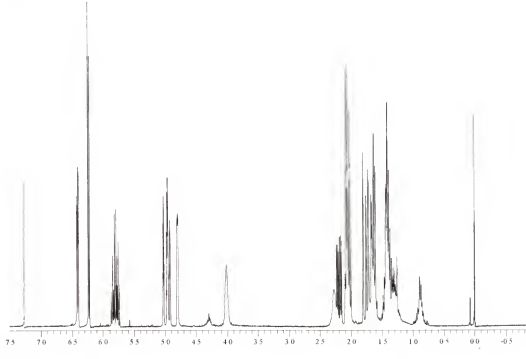
Figure A-30. Spectroscopy data for **360**. A) Structure B) ^{1}H spectrum C) ^{13}C spectrum

A



361

B



C

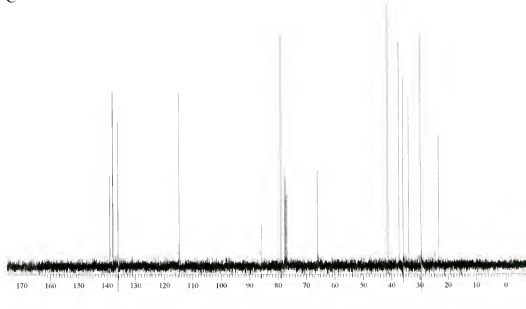
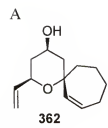
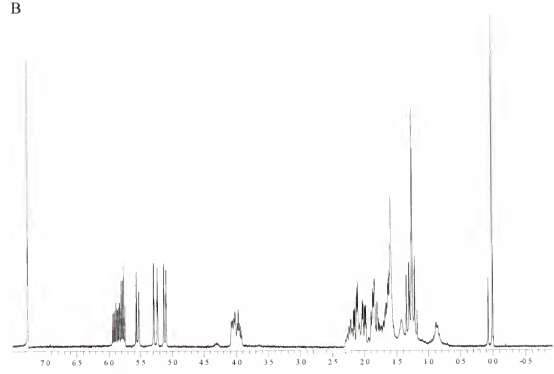


Figure A-31. Spectroscopy data for **361**. A) Structure B) ^{1}H spectrum C) ^{13}C spectrum





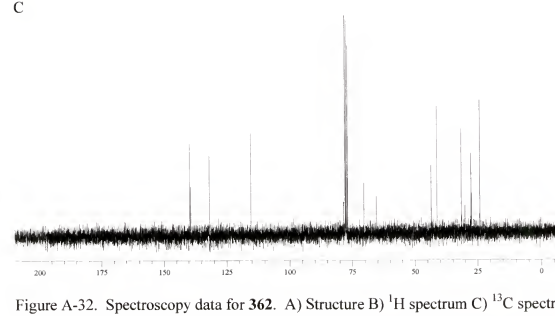
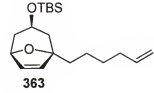


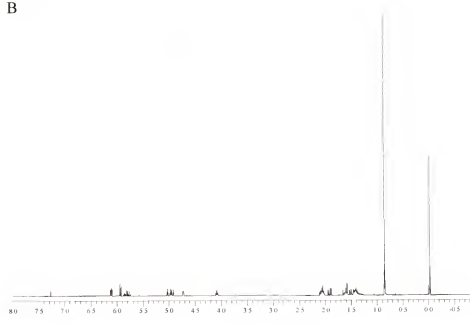
Figure A-32. Spectroscopy data for **362**. A) Structure B) ^{1}H spectrum C) ^{13}C spectrum

A



363

B



C

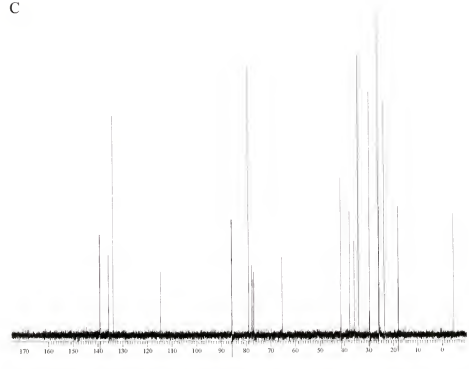
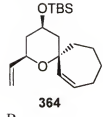


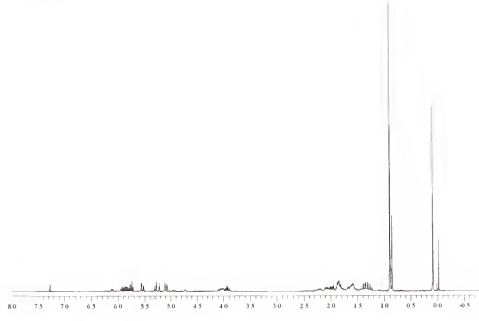
Figure A-33. Spectroscopy data for **363**. A) Structure B) ^{1}H spectrum C) ^{13}C spectrum

A



364

B



C

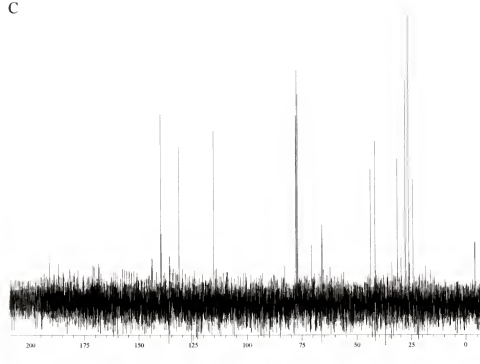
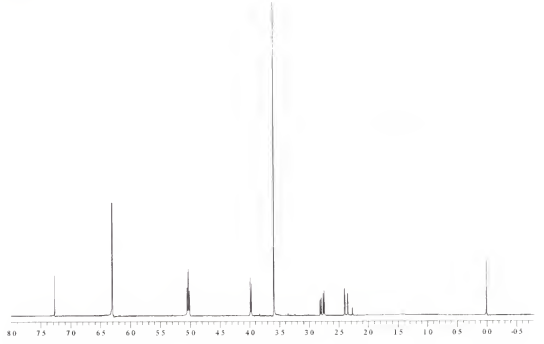


Figure A-34. Spectroscopy data for **364**. A) Structure B) ^{1}H spectrum C) ^{13}C spectrum

A

369

B



C

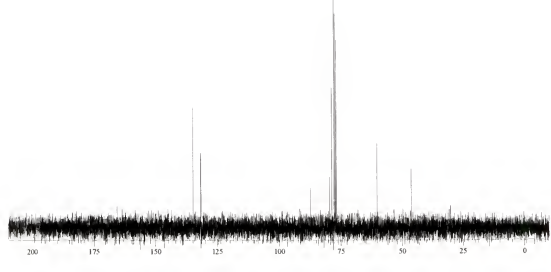
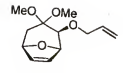


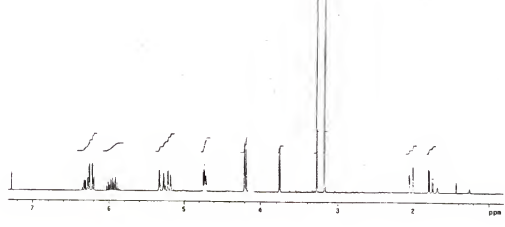
Figure A-35. Spectroscopy data for **369**. A) Structure B) ^{1}H spectrum C) ^{13}C spectrum

A



371

B



C

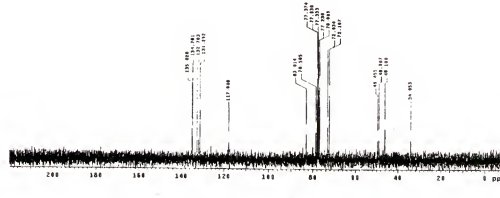
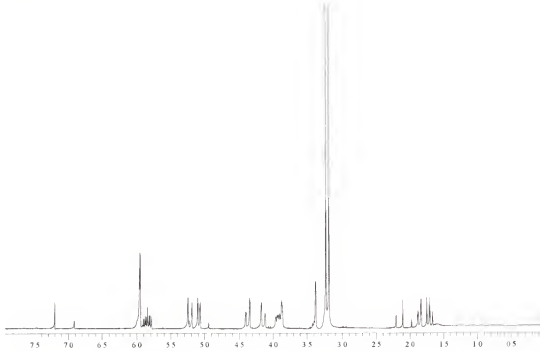


Figure A-36. Spectroscopy data for **371**. A) Structure B) ^{1}H spectrum C) ^{13}C spectrum

A

372

B



C

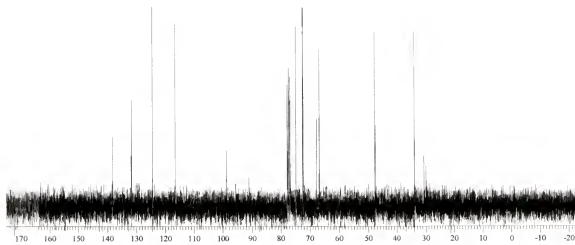
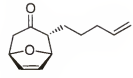


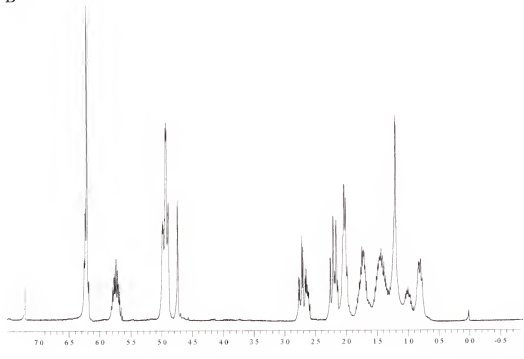
Figure A-37. Spectroscopy data for **372**. A) Structure B) ^{1}H spectrum C) ^{13}C spectrum

A



375

B



C

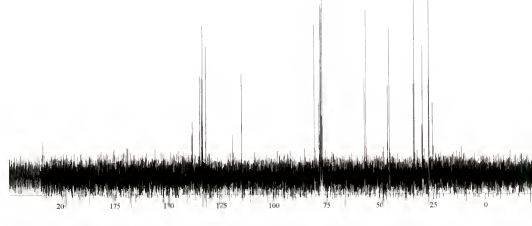


Figure A-38. Spectroscopy data for **375**. A) Structure B) ^{1}H spectrum C) ^{13}C spectrum

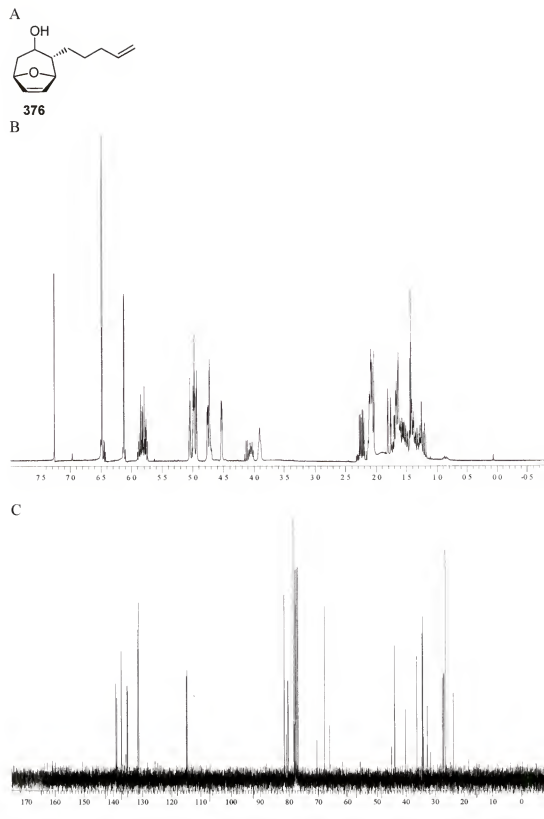


Figure A-39. Spectroscopy data for **376**. A) Structure B) ^{1}H spectrum C) ^{13}C spectrum

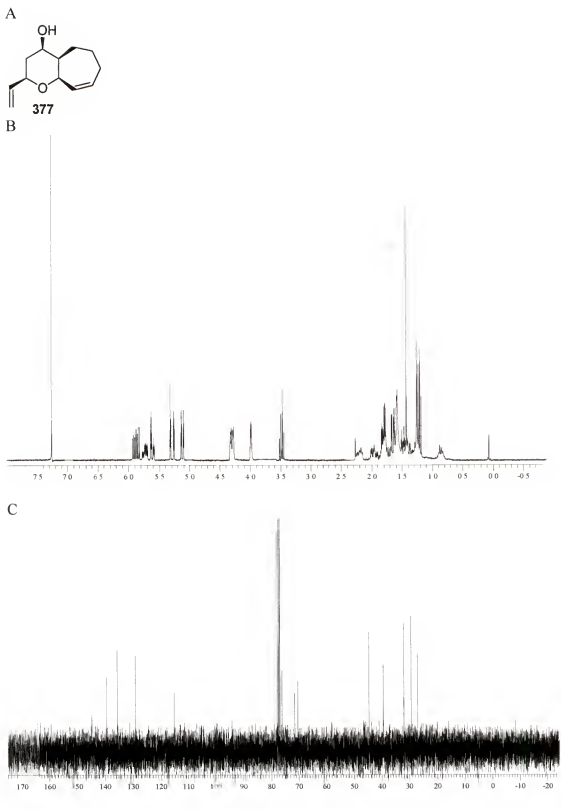
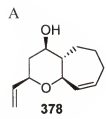
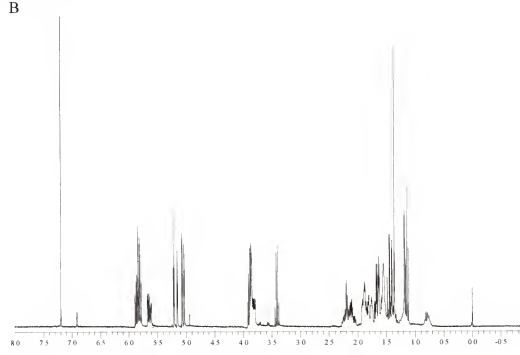


Figure A-40. Spectroscopy data for **377**. A) Structure B) ^{1}H spectrum C) ^{13}C spectrum





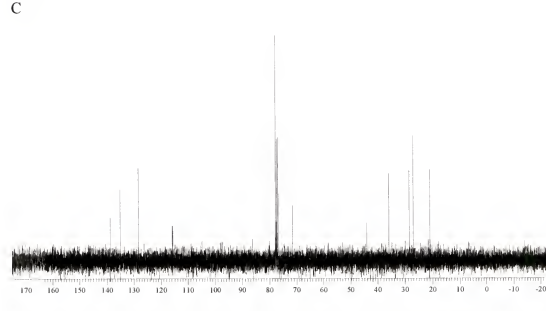


Figure A-41. Spectroscopy data for **378**. A) Structure B) ^{1}H spectrum C) ^{13}C spectrum

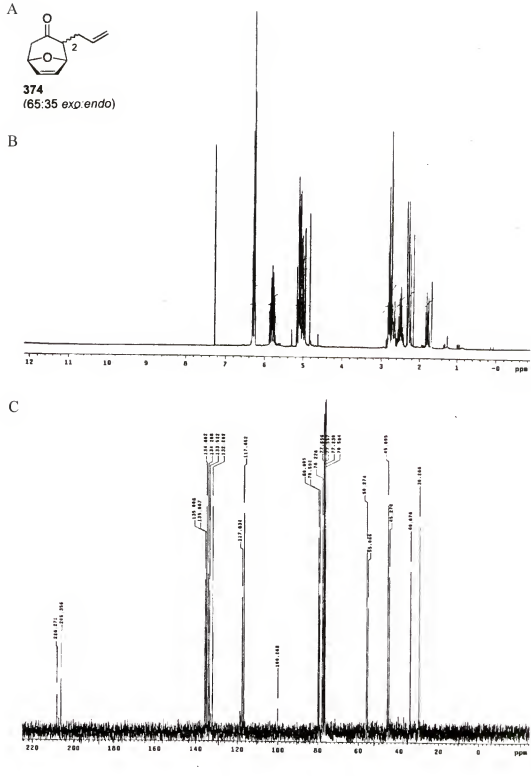
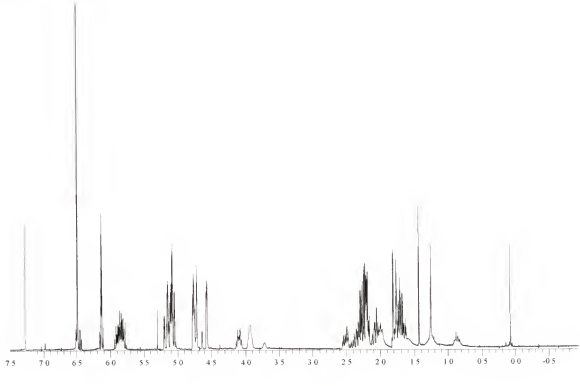


Figure A-42. Spectroscopy data for **374**. A) Structure B) ^{1}H spectrum C) ^{13}C spectrum

A

387

B



C

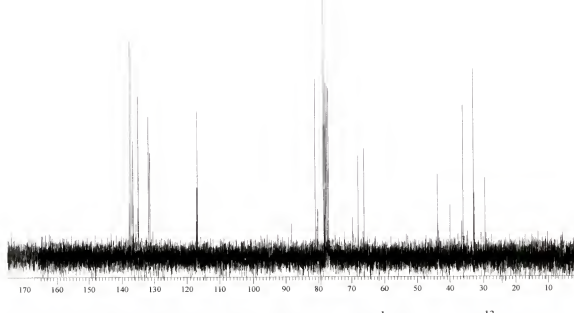


Figure A-43. Spectroscopy data for **387**. A) Structure B) ^{1}H spectrum C) ^{13}C spectrum

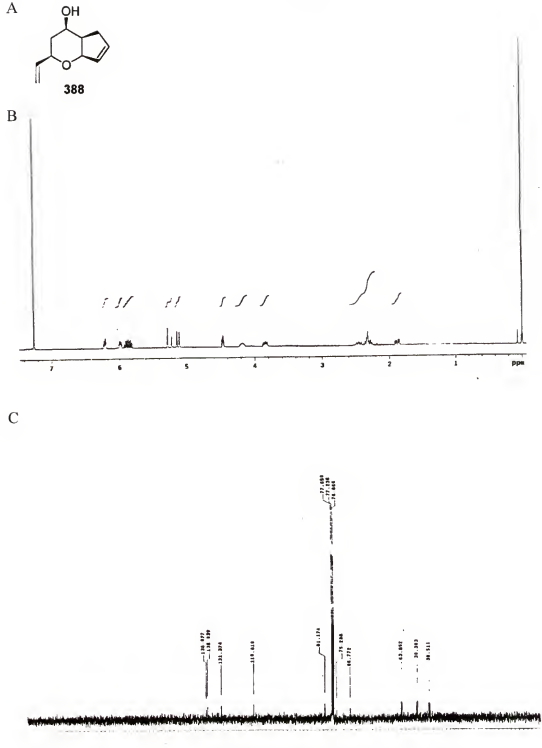
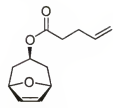


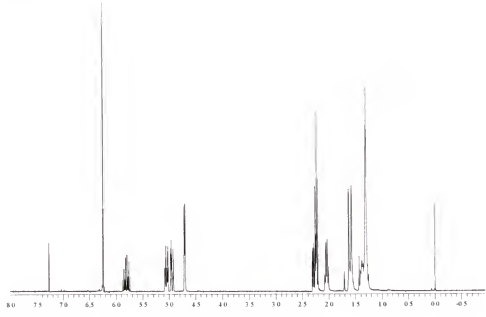
Figure A-44. Spectroscopy data for **388**. A) Structure B) ^{1}H spectrum C) ^{13}C spectrum

A



393

B



C

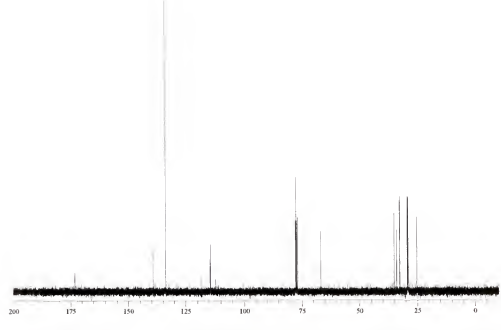
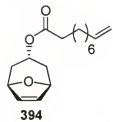


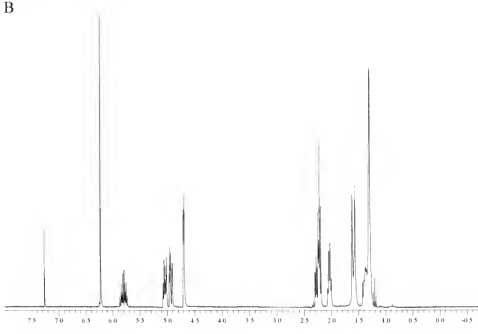
Figure A-45. Spectroscopy data for **393**. A) Structure B) ^{1}H spectrum C) ^{13}C spectrum

A



394

B



C

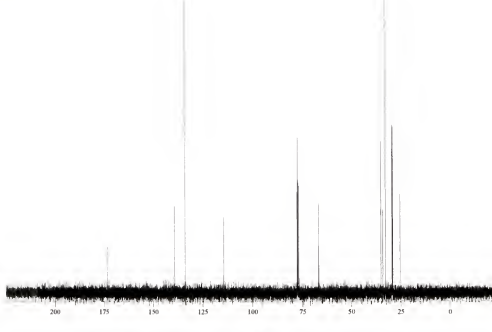


Figure A-46. Spectroscopy data for **394**. A) Structure B) ^{1}H spectrum C) ^{13}C spectrum

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BIOGRAPHICAL SKETCH

Lynn C. Usher was born in Belize City, Belize on December 9, 1977 to Charles and Marjorie Usher. She is the second child of four. In 1996, after earning an associate degree from St. John's College, Sixth Form in Belize City and completing A level examinations in Biology and Chemistry, she went on to obtain a Bachelor of Arts in chemistry from the College of the Holy Cross in Worcester, MA. While at Holy Cross, she did undergraduate research in organic chemistry with Dr. Timothy Curran and completed a semester internship with Dr. Kai Lin in the Department of Pharmacology and Molecular Toxicology at the University of Massachusetts, Medical Center in Worcester. She spent one year at Pfizer before enrolling at the University of Florida in 1999 to pursue a PhD in organic chemistry with Dr. Dennis L. Wright. Upon completion of her degree, she accepted a postdoctoral position with Dr. John Bixby at the University of Miami, School of Medicine where she will work with the Miami Project to Cure Paralysis.

I certify that I have read this study and that in my opinion it conforms to acceptable standards of scholarly presentation and is fully adequate, in scope and quality, as a dissertation for the degree of Doctor of Philosophy.

Dennis L. Wright
Assistant Professor of Chemistry

I certify that I have read this study and that in my opinion it conforms to acceptable standards of scholarly presentation and is fully adequate, in scope and quality, as a dissertation for the degree of Doctor of Philosophy.

Tomas Hudlicky
Professor of Chemistry

I certify that I have read this study and that in my opinion it conforms to acceptable standards of scholarly presentation and is fully adequate, in scope and quality, as a dissertation for the degree of Doctor of Philosophy.

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I certify that I have read this study and that in my opinion it conforms to acceptable standards of scholarly presentation and is fully adequate, in scope and quality, as a dissertation for the degree of Doctor of Philosophy.

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This dissertation was submitted to the Graduate Faculty of the Department of Chemistry in the College of Liberal Arts and Sciences and to the Graduate School and was accepted as partial fulfillment of the requirements for the degree of Doctor of Philosophy.

August 2003

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